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IN THIS ISSUE

Van die Redaksie : Editorial

Behandeling van Tuberkulose met Derivate van Isonikotiensuur
Treatment of Tuberculosis with the Isonicotinic Acid Derivatives
Original Articles

The Senecio Alkaloids
Dermatoses from Cosmetics
Porphyria

New Preparations and Appliances
Correspondence

Passing Events
Association News : Verenigingsnuus

Support Your Own Agency Department (P. xxxd)
Ondersteun u Eie Agenskap-Afdeling (Bl. xxxd)
Professional Appointments (Pp. xxxd-xxxiv)



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CONTENTS

The Senecio Alkaloids. Dr. N. Sapeika	485	Porphyria. Dr. P. W. J. Keet	493
New Preparations and Appliances: Prantal Methylsulphate Tablets	488	Association News: Verenigingsnuus. Griqualand West Branch: Meeting held on 8 May 1952, at the School for the Physically Handicapped, Diskobolos	498
Van die Redaksie: Behandeling van Tuberkulose met Derivate van Isonikotiensuur	489	Passing Events	498
Editorial: Treatment of Tuberculosis with the Isonicotinic Acid Derivatives	489	Correspondence: Cyst-Hepatic Duct (Dr. R. Singer); Benign Gastric Ulcers and Radio-Active Iodine (Dr. M. Weinbren); Hysterectomy (Dr. B. Murless)	499
Dermatoses from Cosmetics. Dr. G. Garnier and Dr. J. Marshall	490		

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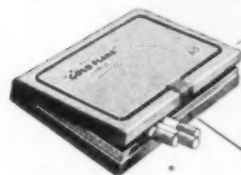


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THE SENECIO ALKALOIDS

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The *Senecio* plants and their alkaloids are of great interest in biology and medicine, particularly in South Africa, where they have been known for many years to produce liver damage in animals and man, and have recently been incriminated as a possible cause of primary liver carcinoma in the Bantu.

Senecio is the largest genus of the plant family Compositae, more than 1,000 varieties having been found all over the world, and at least 300 varieties being widely distributed in South Africa. A few species have been used empirically in some countries in the treatment of various ailments; *Senecio aureus* was actually official in the National Formulary (U.S.A.) 1926. In South Africa Natives have long used various species indiscriminately from childhood intermittently throughout life for numerous disorders. The more important varieties present in this country have been discussed.¹⁻⁴ The distribution in various countries has also been given.⁵⁻⁷

Many of the plants have been shown to contain alkaloids of the pyrrolizidine group and similar alkaloids have been found in the genera *Heliotropium* and *Trichodesma* (Boraginaceae) and in several species of *Crotalaria* (Leguminosae). A list of the better-known alkaloids and their sources is given in Table I. A relatively small number of the alkaloids has so far been investigated and amongst other actions to be described below most have been shown to produce liver damage in experimental animals such as cattle, mice, rats, hamsters and monkeys.

Ingestion of certain *Senecio* plants has long been known to cause liver damage which may result in death in cattle and horses in South Africa (Molteno sickness; Dunsiekte), as also in other countries, e.g. New Zealand (Winton disease), Nova Scotia (Pictou disease), N. America, Canada and Norway. Cases of 'bread poisoning' in human beings have also been described in South Africa. *Senecio* species growing wild on cornfields, e.g. *S. ilicifolius* in the S.W. Cape District have been harvested with the corn and through improper winnowing have led to poisoning, the features of which are described later. To prevent poisoning from this source it is laid down in the Foods, Drugs and Disinfectants Act (No. 13 of 1929):

'Every mill in which grain is milled for human consumption shall be provided with efficient sieving and winnowing appliances so as completely to remove the seeds of *Senecio*

(Sprinkaanbos), and every other poisonous or unwholesome seeds or matter. Any person selling any flour or meal containing such seeds or matter shall be guilty of an offence.'

Senecio ilicifolius and *Senecio burchelli* are proclaimed weeds in the Cape Province under Proclamation No. 117 of 1941, in pursuance of the Noxious Weed Act, No. 42 of 1937.

It is of interest that in the N.W. Cape Districts another form of 'bread poisoning' has occurred due to the weed *Argemone Mexicana* Linn (Mexican poppy, Steekbossie) which grows on wheatlands and causes epidemic dropsy when contaminated wheat is eaten^{8,9}; the poison appears to be argemone oil and the effects due to damage to the capillary wall.

CHEMICAL PROPERTIES

The *Senecio* alkaloids have been studied from the chemical standpoint by many workers.^{10,12} In South Africa the constitution of isatidine and other related alkaloids has been investigated by de Waal.¹⁴⁻¹⁶

The *Senecio* alkaloids are colourless, optically active, crystalline compounds, bitter in taste, and mostly soluble except for example isatidine. They form salts readily, such as hydrochlorides and nitrates. A few of the alkaloids are isomeric, e.g. senecionine, squalidine, integerrimine. According to de Waal¹⁶ pterophine is probably identical with seneciphylline, but Harris *et al.*¹⁰ found important differences in their action. An alkaloid aquaticine has been isolated from *S. aquaticus* by Evans and Evans¹⁷ and senkirkine from *S. kirkii* by Briggs *et al.*¹⁸

By employing a chromatographic fractionation procedure the alkaloids from *S. carthamoides*, *douglasii*, *eremophilus*, and *ampullaceus* have been shown¹⁹ to be mixtures of some or all of the alkaloids α -longilobine, β -longilobine, senecionine and riddelline.

On alkaline hydrolysis most of the alkaloids yield acids called 'necic acids' and necines. Most of the alkaloids yield the amino-alcohol called retronecine or necines closely related to it.¹³

Retronecine is present in many of the alkaloids including retrorsine, pterophine, senecionine, scleratinine, integerrimine, jacobine, longilobine, riddelline, seneciphylline, and hieracifoline, and also in monocrotaline (from *Crotalaria spectabilis* and *Crotalaria retusa*). As retrone-

cine and retronecic lactone given in large doses intravenously cause death in mice or rats but fail to

produce liver lesions,¹⁰ the hepatotoxic action of the Senecio alkaloids would appear to reside in the intact molecules. The degradation products also do not produce hypoprothrombinaemia in rats.²⁰

From *Boraginaceae* species an alkaloid was obtained²¹ which on hydrolysis yielded a base heliotridine which is isomeric with retronecine, and retronecine was apparently also obtained from an alkaloid trichodesmine from a related species of plant.²²

It is interesting that the alkaloid lasiocarpine $C_{11}H_{17}O_2N$ obtained from *Heliotropium lasiocarpum* produces hepatic lesions similar to those produced by most alkaloids of Senecio species.²³ The alkaloid monocrotaline obtained from *Crotalaria spectabilis* and *C. retusa* resembles the Senecio alkaloids and on hydrolysis yields monocrotic acid and retronecine.¹⁰

ACTIONS

The actions of several crystalline alkaloids have been studied in mice, rats, guinea-pigs, the Syrian hamster and monkeys.

Toxicity. The median lethal doses of alkaloids injected intravenously in mice have been determined²³⁻²⁶ and are shown in Table 2. Large doses cause rapid respiration,

TABLE 2

Alkaloid	Median Lethal Dose \pm Standard Error
	(mg. per kgm.)
Pterophine	58.13 \pm 3.73
Retrorsine	58.8 \pm 5.3
Senecionine	64.12 \pm 2.24
Carthamoidine ..	68.32 \pm 2.44
Jacobine	77.11 \pm 2.86
Longilobine	77.85 \pm 3.33
Integerrimine ..	78.32 \pm 3.05
Spartioidine	80.39 \pm 1.93
Seneciphylline ..	88.12 \pm 5.45
Riddelline	104.9 \pm 4.15
Sceleratine	139.4 \pm 9.33
Isatidine	834.5 \pm 50.25
Retronecine	634.0 \pm 26.0

clonic convulsions and death in a few minutes, but smaller doses cause lethargy and death in some animals in 24 to 96 hours. Ascites, pulmonary oedema, hydrothorax, and necrosis of lymphocytes in spleen and thymus were observed at autopsy, and liver damage (to be considered below in more detail).

Liver Damage. In mice senecionine, integerrimine, jacobine, longilobine, spartioidine, sceleratine, isatidine, seneciphylline and riddelline produce hepatic necrosis which is chiefly central, whereas with carthamoidine and pterophine it is predominantly peri-portal. In mice retrorsine produces central and peri-portal damage, but in guinea-pigs no visceral changes were observed.²⁴ Longilobine has recently been shown to contain two fractions both of which cause liver damage.²⁷ It is of interest that platyphylline produced no liver damage in mice, in rats or in guinea-pigs.²³ Retronecine, which is present in many of the alkaloids, sometimes produced rapid death but no hepatic injury. Thus the hepatotoxic action of the alkaloids appears to reside in the intact alkaloid

TABLE 1

Senecio Alkaloid	Empirical Formula	Source
Aquaticine	$C_{18}H_{21}O_3N$	<i>S. aquaticus</i>
Campestrine	$C_{18}H_{21}O_3N$	<i>S. campestris</i> var. <i>maritimus</i>
Carthamoidine ..	$C_{18}H_{21}O_3N$	<i>S. carthamoides</i>
Fuchsisenecionine ..	$C_{18}H_{21}O_3N$	<i>S. fuchsii</i>
Graminifoline	$C_{18}H_{21}O_3N$	<i>S. graminifolius</i>
Hygrophylle	$C_{18}H_{21}O_3N$	<i>S. retrorsus</i>
Integerrimine	$C_{18}H_{21}O_3N$	<i>S. hygrophilus</i> <i>S. integerrimus</i>
Isatidine	$C_{18}H_{21}O_3N$	<i>S. isatideus</i> <i>S. retrorsus</i> <i>S. sceleratus</i>
Jacobine	$C_{18}H_{21}O_3N$	<i>S. jacobea</i> <i>S. cineraria</i> <i>S. erucifolia</i> <i>S. jacobea</i>
Jacodine	$C_{18}H_{21}O_3N$	<i>S. aquaticus</i> <i>S. cineraria</i>
Jaconine	$C_{18}H_{21}O_3N$	<i>S. jacobea</i>
Langerosine	$C_{18}H_{21}O_3N$	<i>S. retrorsus</i> <i>S. longilobus</i> <i>S. douglasii</i>
Longilobine	$C_{18}H_{21}O_3N$	<i>S. carthamoides</i> <i>S. eremophilus</i> <i>S. ampullaceus</i> <i>S. mikanioides</i> <i>S. othonnae</i>
Mikanoidine	$C_{18}H_{21}O_3N$	<i>S. platyphyllus</i>
Othosenine	$C_{18}H_{21}O_3N$	<i>S. adnatus</i> <i>S. hygrophilus</i> <i>S. pterophorus</i>
Platyphylline	$C_{18}H_{21}O_3N$	<i>S. ilicifolius</i> <i>S. glaberrimus</i> <i>S. retrorsus</i> <i>S. ilicifolius</i> <i>S. pterophorus</i>
Pterophine	$C_{18}H_{21}O_3N$	<i>S. sceleratus</i> <i>S. graminifolius</i> <i>S. isatideus</i> <i>S. latifolius</i> <i>S. venosus</i>
Retrorsine	$C_{18}H_{21}O_3N$	<i>S. riddellii</i> <i>S. hygrophilus</i> <i>S. brachypodus</i>
Riddelline	$C_{18}H_{21}O_3N$	<i>S. rosmarinifolius</i> <i>S. sceleratus</i> <i>S. adnatus</i> <i>S. paucilingulatus</i>
Rosmarinine	$C_{18}H_{21}O_3N$	<i>S. sceleratus</i> <i>S. retrorsus</i> <i>S. latifolius</i> <i>S. retrorsus</i> <i>S. latifolius</i> <i>S. retrorsus</i> <i>S. ilicifolius</i> <i>S. integerrimus</i> <i>S. vulgaris</i> <i>S. aureus</i> <i>S. jacobea</i> <i>S. squalidus</i> <i>S. viscosus</i> <i>S. platyphyllus</i> <i>S. stenoccephalus</i> <i>S. spartioides</i> <i>S. kirkii</i> <i>S. sylvaticus</i> <i>S. spartioides</i> <i>S. squalidus</i>
Sceleratine	$C_{18}H_{21}O_3N$	
Senecifolidine	$C_{18}H_{21}O_3N$	
Senecifoline	$C_{18}H_{21}O_3N$	
Senecionine	$C_{18}H_{21}O_3N$	
Seneciphylline	$C_{18}H_{21}O_3N$	
Senkirkine	$C_{18}H_{21}O_3N$	
Silvasenecine	$C_{18}H_{21}O_3N$	
Spartioidine	$C_{18}H_{21}O_3N$	
Squalidine	$C_{18}H_{21}O_3N$	

molecule.¹⁰ With repeated doses of the alkaloids given orally, subcutaneously or intravenously to mice cirrhosis was not produced; cattle, cows and horses that have eaten *Senecio* plants have been reported to have developed cirrhosis. Mice which ingested the dried plant *S. riddellii* developed cirrhosis whereas the alkaloid-free resinous residue produced gangrene of the digestive tract and no hepatic cirrhosis.^{28, 29}

In rats retrorsine was considered to produce liver damage through a primary vascular action, probably on branches of the hepatic veins³⁰; similar changes in the liver vessels were described in horses suffering from 'dunsiekte'.³¹ Retrorsine was also found to produce a primary toxic effect both on liver cells and on central and hepatic veins in the rat, leading to centrilobular haemorrhagic necrosis.³² What appeared to be endothelial proliferation might be macrophages swept in from surrounding tissues or produced locally by the vascular endothelium; these cells may be replaced by fibrous tissue. The appearance observed in human cases and in horses might be produced in this way. Any primary liver damage becomes masked by the secondary effects of the vascular lesions. A protein deficient diet was found to enhance markedly the effect of retrorsine on rat liver. Another study³³ of the influence of age, sex and diet upon the lethal effects of monocrotaline in rats concluded that the greater susceptibility of animals on a deficient diet may be due to the metabolic effects of male sex hormones.

The plasma prothrombin time of rats has been shown to be prolonged (hypoprothrombinaemia) after the administration of certain alkaloids, e.g. senecionine, retrorsine, pterophine, scleratinine, spartioidine.³⁰ A decrease in the ascorbic acid concentration of the rat liver is produced by pterophine.³⁴

In the Syrian hamster (*Cricetus aureus*) senecionine produces liver necrosis which is predominantly periportal,³⁵ whereas in mice and rats it produces necrosis which is mainly central.

In monkeys (*Macacus rhesus*) pterophine produces periportal necrosis, and senecionine produces increase of prothrombin time and serum bilirubin associated with liver necrosis.³⁵

Various hypotheses advanced to explain the hepatotoxic action of the alkaloids on the basis of an action on the vessels or primary liver damage have recently been discussed by Selzer and Parker.³⁶

Liver Tumours. In previous work cited above survival of animals has never exceeded 3 months. However, Cook *et al.*³⁷ were able to examine the livers of albino rats after more than 8 months by the intermittent addition to their drinking water of the alkaloids extracted from *S. jacobaea* L. They observed necrosis and degenerative changes followed by nodular hyperplasia of liver cells or tumour-like masses showing the characters of hepatomas and excessive proliferation of bile duct epithelium. No metastases or tumours of other organs were found. The lesions are similar to some of those produced by *p*-dimethyl amino-azo benzene (butter yellow). Deficient diet is apparently not alone sufficient to induce the liver tumour, for in newly weaned albino rats fed up to 15 months with maize-meal porridge (mealie pap) and sour milk, the staple diet of the Bantu, severe liver injury but not liver tumours has been observed.^{38, 39} The high

incidence of primary liver cancer among the Bantu in South Africa has suggested that some extrinsic factor is involved.⁴⁰ In view of their findings Cook *et al.*³⁷ suggest that the indiscriminate use by the Bantu of *Senecio* plants for various ailments from childhood intermittently throughout the whole life may possibly have a bearing on the etiology of primary liver tumours in these people. The Bantu remedies may also include other carcinogenic agents; vital information may perhaps be obtained by tactful approach to African herbalists and tribal authorities.

Other Actions. In frogs retrorsine produces weakness and paralysis of the extremities.²⁴ Platyphylline, however, produces convulsions, as also in certain other animals, probably from an action on the medulla.²³ Pterophine in large doses produced no symptoms in frogs.⁴¹

The blood pressure of cats is lowered by the intravenous injection of senecionine, integerrimine, jacobine, longilobine, spartioidine, carthamidine, riddelline, pterophine, retrorsine, and retronecine, whereas scleratinine and isatidine and occasionally seneciophylline produce a slight rise in blood pressure (Chen *et al.*, and Harris *et al.*); the depressor action of pterophine is due mainly to vasodilatation.⁴¹

The isolated intestine of the rabbit is generally inhibited and isolated guinea-pig uterus stimulated by the alkaloids and by retronecine.^{10, 28} Isolated guinea-pig uterus is stimulated by extracts of *S. vulgaris* and *S. jacobaea*.⁴² The uterus in anaesthetized cats is stimulated by pterophine and retrorsine.⁴¹

Hyperglycaemia is produced in unanaesthetized rabbits by retrorsine²⁴ and by pterophine.⁴¹

Mydriasis with loss of light reflex is produced by platyphylline which appears to have an atropine-like action.²³ Pterophine has no action on the pupil.

Senecionine diffuses through the placenta of the pregnant rat and causes degeneration in the livers of the foetuses.⁴³

POISONING

The features of *Senecio* poisoning (seneciosis) occurring under natural conditions and experimentally induced in horses and cattle, and poisoning occurring accidentally in men, have been discussed in the earlier investigations.^{1-4, 31}

In Man the features of poisoning have been described briefly as follows. The onset may be gradual or rapid, with epigastric discomfort, abdominal pain, nausea, vomiting, especially after meals, sometimes with blood; diarrhoea with blood in the stools. Emaciation, ascites and enlarged liver are other features. The majority of patients have died from 14 days to 2 years or longer after the onset of the disease.⁴⁴ Most cases of bread poisoning occurred in the Mossel Bay, George, Riversdale and Clanwilliam districts. Details of cases investigated in Cape Town are given by Selzer and Parker.³⁶ These authors reported that in *Senecio* poisoning in man a striking centrilobular haemorrhagic lesion occurs in the liver from widespread occlusion of the hepatic veins (Chiari's syndrome). This appears to result from proliferation of the intima and in some cases superimposed thrombi undergoing organization; frequently the central and small hepatic veins were necrotic.

The possibility of carcinoma of the liver with all its

varied manifestations being caused by Senecio alkaloids must now be borne in mind in view of the findings of Cook *et al.*³⁷

SUMMARY

Senecio plants (Sprinkaanbos; ragwort) are of great interest and importance. They contain alkaloids of which many have been identified chemically but only a few have been investigated experimentally.

Senecio poisoning has long been known to be a cause of chronic illness and death in cattle and horses, e.g. Molteno disease, dunsiekte, and in man cases of 'bread poisoning' (from meal contaminated with the weed) occurred in previous years in the Mossel Bay, George, Riversdale and Clanwilliam districts until preventive measures were taken.

The features of poisoning were chiefly epigastric discomfort, abdominal pain, nausea, vomiting, diarrhoea, with blood in the stools, emaciation, ascites, and enlarged liver; death occurred in 14 days to 2 years or longer after the onset of the disease.

Many of the alkaloids have been shown to produce liver necrosis in various laboratory animals. Recently, by intermittent feeding of a Senecio plant extract for several months, nodular hyperplasia of liver cells or tumour-like masses showing the character of hepatomas and excessive proliferation of bile duct epithelium have been produced. It has, therefore, been suggested that the high incidence of primary liver carcinoma in the malnourished Bantu may be due to the indiscriminate use of Senecio plants for various ailments from childhood and throughout life. The alkaloids also have other actions.

The subject is fully reviewed in the present article.

Thanks are due to Prof. H. L. de Waal, who provided the pterophine and retrorsine used in our experimental investigations. Expenses of this work were defrayed by a grant from the Staff Research Fund, University of Cape Town, for which grateful acknowledgment is made.

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NEW PREPARATIONS AND APPLIANCES

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Abstract No. 4

T.B.

Fust, B., Priv.-Doz.
Medical Laboratories
F. Hoffmann-La Roche & Co. Ltd. Co.
Basle (Switzerland).

Toxicity. Pharmacology. Chemo-
therapy. Action *in vitro* and *in*
vivo. Comparison with tuberculo-
statics.

Orientierung über das Antituberkulotikum Rimifon "Roche"

Survey of the Antituberculotikum Rimifon "Roche"

Lecture delivered at the Post-Graduate Course of the Zürich Tuberculosis League in Arosa, 6 March 1952

Schweiz. med. Wochenschrift 1952, No. 13, 333—35

In the summer of 1950 Grunberg and Schnitzer discovered the unusual anti-tuberculosis properties of isonicotinylhydrazine, a substance which has recently been made available as Rimifon 'Roche'.

Extensive investigations on experimental animals showed the following results:

Toxicity:

The LD₅₀ (dose causing death in 50% of the experimental animals) upon oral administration was 150 mg./kg. for mice, 250 mg./kg. for rabbits and ca. 1,500 mg./kg. for rats. Acute intoxication causes death through respiratory paralysis. In chronic intoxication trials young rats given 0.5% Rimifon mixed in their food for 13 weeks gained weight at the same rate as the control animals. As a result of various further investigations it can be said that toxicity is of moderate degree although showing appreciable variations between species.

Pharmacology:

In doses of 1-10 mg./kg. Rimifon exerts only moderate pharmacological effects on experimental animals. Slight broncholytic and ganglion-blocking properties were observed.

Chemotherapeutic Action:

The various investigators established a tuberculostatic action *in vitro* of dilutions of 1:20,000,000 to 1:60,000,000 according to the methods used. *In vitro* bovine are less sensitive than human tuberculosis bacilli.

In vivo investigations in the mouse showed that when given by mouth 4.6 mg./kg. Rimifon exerts a 50% anti-tuberculous action on intravenously infected animals; 6.2 mg./kg. was necessary to obtain the same result in nasally infected animals. Activity is even greater upon s.c. administration. A small elevation of the dosage increases the effect to almost 100%. When the lung and liver changes observable by magnifying glass in *i.v.* infected mice treated with Rimifon are compared with those of the untreated control animals, it can be established that Rimifon causes a 75% reduction of the tuberculous pulmonary foci; histological examination showed an 85% regression of lung alterations and 35% regression of liver alterations. In guinea-pigs Rimifon in a daily dosage of 10-20 mg./kg. s.c. is effective against infection with human and bovine tuberculosis bacilli. Concurrent investigations with human tuberculosis bacilli showed that the general incidence of tuber-

culous changes, macroscopic and observed through the magnifying glass, decreased by 65%. Histological examination of the lung and liver demonstrated a 50% and 100% action respectively. Prophylactic experiments against s.c. bovine infections showed 90% general protection; histologically there was 80% and 90% protection in the lung and liver respectively. Computation of the chemotherapeutic index shows that Rimifon is more effective than other preparations:

ANTI-TUBERCULOUS ACTION IN MICE

Preparation	Chemotherapeutic Index = LD ₅₀ : Effective dose 50%	
	Intravenous	Intranasal
Rimifon by mouth	44.1	32.7
Nicotinamide by mouth	4.2	< 1.0
Streptomycin s.c.	38.8	9.7
p-aminosalicylic acid by mouth	3.0	< 1.0
p-acetylaminobenzaldehyde- thiosemicarbazone by mouth	16.5	1.0
Isonicotinaldehyde- thiosemicarbazone by mouth	20.6	7.6

Tuberculosis bacilli could no longer be cultivated from the lungs of *i.v.* infected mice treated with 10-25 mg./kg. Rimifon daily. The bactericidal action of Rimifon is further confirmed by the observation that *i.v.* infected mice treated with Rimifon for 3 weeks and then given no treatment for a further 3 weeks, showed no or only slight signs of tuberculosis when autopsied on the 42nd day. Similar investigations with previous tuberculostatics showed that after discontinuation of the therapy they no longer protected against progress of the infection nor against death.

The action of Rimifon appears to be directed specifically against tuberculosis bacilli because experimental infections with hemolytic streptococci, pneumococci, *Salmonella schottmülleri*, *Trichomonas vaginalis*, *Trypanosoma equiperdum* or influenza virus were not influenced.

The lecture also reports on the first clinical trials on tuberculosis in human subjects carried out at Sea View Hospital, the Tuberculosis Treatment Centre of New York City. The results are extraordinarily encouraging, and justify further testing of Rimifon 'Roche' on the widest basis.

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*Gruber, C. M., Ellis, F. W. and Freedman, G.:
J. Pharmacol. and Exper. Therap. 81:254 (July) 1944.

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South African Medical Journal

Suid-Afrikaanse Tydskrif vir Geneeskunde

VAN DIE REDAKSIE

BEHANDELING VAN TUBERKULOSE MET DERIVATE VAN ISONIKOTIENSUUR

Onlangs was daar voorbarige publisiteit in die lekepers vir 'n nuwe behandeling van tuberkulose met die hidrasien-derivate van isonikotiensuur. Verregaande eise omtrent 'wonder geneesmiddels' met wonderbaarlike hoedanighede is gemaak. Dit is in elke sin van die woord betreuenswaardig. Die internis word gedwing om 'n behandeling voor te skryf, die aansprake waarvoor op die oomblik met gepaste voorbehoud aanvaar moet word. Wat nog erger is, is die ongeoorloofde verwekking van hoop op herstel by pasiënte en hulle verwante.

Die feite is dat hierdie nuwe derivate baie duidelike, inderdaad merkwaardige aktiwiteit getoon het wanneer dit teen die tering-organisme *in vitro* getoets word; maar, hoewel daar bemoedigende resultate by die mens verkry is, is ons nog nie in staat om voldoende dosisse voor te skryf of te voorspel wat die eindresultaat sal wees nie.

In die Verenigde State van Amerika is die nuwe geneesmiddels nog nie in die handel tussen state beskikbaar nie, en internis in daardie land is aangeraai om hulle pasiënte mee te deel dat verdere navorsing nodig is om die waarde van die middels te bepaal. Een van die omvattende ondersoeke is in die Sea View-hospitaal op Staten Eiland uitgevoer. Voorlopige verslae is in die *Quarterly Bulletin of Sea View Hospital*,¹ 'n tydskrif wat hom aan tuberkulose en kroniese borskwale wy, gepubliseer. Pasiënte wat nie op die behandeling met streptomisien, PAS en ander middels gereageer het nie, is met die hidrasien-derivate behandel. Die kliniese resultate was bevredigend. Die sistematiese manifestasies van die teringproses was spoedig onder beheer; koors en giftige simptome het bedaar, eetlus het teruggekeer en daar was 'n merkwaardige gewigstoename. Hierdie veranderings het vinnig, seker en tot so 'n mate soos ons nooit by ander chemoterapeutiese of antibiotiese middels bespeur het nie, voorgekom. By beperkte studies het ons ook 'n opvallende uitwerking op die plaaslike anatomiese longletsel opgemerk, wat deur sommige radiologiese veranderings bewys is; aansienlike afname van hoers en spuwing by ongeveer een derde van die gevalle en 'n oënsynlike, ten minste tydelike, verandering na negatief van die spuug, by bakteriologiese toets, is ook bespeur. Ons het ook belangrike chemoterapeutiese uitwerkinge op buite-longtering met inbegrip van die harsing- en rugmurgvlies, oor- en keelholte, strottehoof, ens., opgemerk. Hierdie uitwerkinge is ook in 'n groter mate opgemerk as by ons vorige ondervindings met ander antibiotiese en chemoterapeutiese middels. In die afwesigheid van aansienlike giftigheid is die isonikotiensuur hidrasien en sy derivate 'n belangrike groep chemo-

EDITORIAL

TREATMENT OF TUBERCULOSIS WITH THE ISONICOTINIC ACID DERIVATIVES

There has recently been premature publicity in the lay press for a new treatment of tuberculosis with the hydrazine derivatives of isonicotinic acid. Unwarranted claims about 'wonder drugs' with miraculous properties have been made. This is regrettable in every sense. The hand of the physician is forced to introduce a treatment, the claims for which must be accepted at the present time with due reserve. Even more serious is the unjustified raising of hope in patients and their relatives.

The facts are that these new derivatives have shown a very definite, indeed remarkable, activity when tested against the tubercule organism *in vitro*; but, although encouraging results have been obtained in man, we are not yet in a position to define adequate dosage or to prognose about the ultimate results achieved.

In the United States of America the new drugs are not yet available in interstate commerce, and in that country physicians have been advised to inform their patients that more studies are needed to evaluate the position. One of the most comprehensive investigations has been done at the Sea View Hospital on Staten Island. Preliminary reports have been published in the *Quarterly Bulletin of Sea View Hospital*,¹ a journal devoted to tuberculosis and chronic pulmonary diseases. Patients not responding to Streptomycin, PAS and other measures, were treated with the hydrazine derivatives. The clinical results were gratifying. The systemic manifestations of the tuberculous process were rapidly brought under control; fever and toxic symptoms subsided, appetite was recovered and there was a remarkable gain in weight. These changes occurred with a rapidity, a certainty and to a degree which we have never observed in other chemotherapeutic or antibiotic agents. In limited studies, we have also observed a marked effect on the local, anatomical pulmonary lesion, evidenced by some radiological changes, marked reduction in cough and expectoration in about one-third of the cases and an apparent, at least temporary, conversion of the sputum to negative on bacteriological examination. We have also observed important chemotherapeutic effects on extra-pulmonary tuberculosis, including meningeal, oropharyngeal, laryngeal, etc. These effects, too, have been noted in a fashion superior to our previous experiences with other antibiotic and chemotherapeutic agents. In the absence of significant toxicity, the isonicotinic acid

terapeutiese middels teen menslike tering en vereis uitgebreide ondersoek.²

Dit wil ongetwyfeld voorkom asof die hidrasien-derivate 'n spesifieke middel is teen die teringkiem, maar dit sal ons baat om kennis te neem van die versigtige waarskuwing uitgereik deur Groot-Brittanje se Ministerie van Gesondheid. Dit vestig die aandag op die dwaasheid om hierdie sterk geneesmiddel onoordeelkundig te gebruik. Die Ministerie van Gesondheid sê: „Dis geensins seker dat dit skadeloos is nie; inderdaad, eksperimente met diere toon die moontlikheid van giftigheid, veral wanneer die middel vir 'n aansienlike tyd gebruik word. By die mens is daar min of niks bekend oor langdurige giftigheid nie. Nog 'n sterk rede teen onoordeelkundige gebruik is die moontlikheid dat rasse van die teringkiem wat weerstand bied by die gemeenskap sal ontwikkel. Niks hiervan is tot dusver by die mens bekend nie, maar dis bekend dat sulke rasse in die laboratorium kan ontwikkel. Dit wil voorkom asof dit verstandig sou wees om voorlopig die gebruik daarvan te beperk tot die behandeling van binne-pasiënte in sulke hospitale wat oor 'n volle laboratorium-diens beskik.“³

Die hidrasien-derivate is nou in Suid-Afrika beskikbaar en dis wenslik dat die gebruik daarvan in die Unie sorgvuldig beheer moet word en dat die resultate gekorreleer word met dié wat behaal is in kliniese toetse wat op die oomblik in die Verenigde State, Switserland en deur die Mediese Navorsingsraad in Groot-Brittanje plaasvind.

Om versigtigheid aan te beveel, beteken egter nie dat ons die besef uit die oog verloor dat ons miskien op die voorraand van 'n nuwe terapeutiese era in die behandeling van tuberkulose staan nie.

hydrazide and its derivatives are an important group of chemotherapeutic agents for human tuberculosis and require extensive investigation.²

There undoubtedly appears to be a remarkable specificity of the hydrazine derivatives for the tubercle bacillus, but we would be well advised to take note of the cautious warning issued by the Ministry of Health in Great Britain. This draws attention to the unwisdom of using this potent drug indiscriminately. The Ministry of Health states: „It is by no means certain that it is harmless: indeed, animal experiments indicate the possibility of toxicity, particularly when the drug is used for a considerable time. In man little or nothing is known of long-term toxicity. Another strong reason against indiscriminate use is the possibility of developing resistant strains of tubercle bacilli in the community. Nothing is known of this in man yet, but it is known that such strains can develop in the laboratory. It would seem prudent for the present to limit its use to the treatment of in-patients in such hospitals as are equipped with a full laboratory service.“³

The hydrazine derivatives have now become available in South Africa, and it is desirable that their use in the Union should be carefully controlled and the results correlated with those obtained in the clinical trials at present being conducted in the United States, in Switzerland and by the Medical Research Council in Great Britain.

To commend caution, however, is not to fail to recognize that we may be on the threshold of a new therapeutic era in the treatment of tuberculosis.

2. Selikoff, I. J., Robitzek, H. and Ornstein, G. G. (1952): Quart. Bull. Sea View Hosp., 13, 27.
3. Lancet (1952): I, 713.

2. Selikoff, I. J., Robitzek, H. and Ornstein, G. G. (1952): Quart. Bull. Sea View Hosp., 13, 27.
3. Lancet (1952): I, 713.

DERMATOSIS FROM COSMETICS

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Among the substances capable of producing dermatoses the cosmetics hold a high place. It is important to remember this possibility and to know the methods used in determining the causative agent or agents, as rapid cure can be obtained by removal of the cause, but seldom by non-specific measures.

The cutaneous accidents resulting from the use of cosmetics are usually due to sensitization; in other words the noxious agent, the allergen, is not a primary irritant (at least in the concentration used in the cosmetic) and the quantity required to produce a reaction varies from one person to the next. The skin reactions produced by different substances are identical and the most important factor is the terrain on which the reaction takes place. Individual factors may be:

1. Cutaneous predisposition in certain subjects. Sufferers from atopic dermatitis or the allied conditions of hay fever and asthma are more liable to be affected than are people with no previous history of allergic diseases. Seborrhoeic dermatitis can also be a predisposing factor.

2. The emotional state of the individual is recognized as being capable of influencing the appearance and progress of attacks of allergic diseases.

3. Hormonal imbalance may be a factor in some cases.

The artificial dermatoses to be discussed have a regional and tissular character. It has to be remembered, however, that once the reaction has been produced at the site of application there may be secondary reactions at a distance, in places where the allergen has not been applied; and this may confuse the observer who is unaware of the possibility. It is also essential to know that sensitization to a cosmetic product is a persistent and probably perma-



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ment state and that it may lead to cross-sensitization to other substances of related chemical structure. Such group sensitivity may operate for products to which the patient was previously insensitive. Thus a woman who has become sensitive to a hair dye containing paraphenylenediamine may become, in consequence, sensitive to local anaesthetics, sulphonamides or synthetic rubber.

Evidence of sensitization to cosmetics rarely appears immediately after the first application; there is usually a latent period lasting weeks, months or even years during which the substance is used daily or intermittently without ill effects. The fact that a certain cosmetic has been used with impunity for a considerable time is not, therefore, a point against considering it in the course of investigation.

Hair Dyes. By far the most important causes of sensitization to hair dye are paraphenylenediamine and similar related synthetic organic compounds. The first symptom, an intense itch, usually appears within a day of the

relatively rare. If the application of the product is too prolonged it can lead to breaking of the hair, and in exceptional cases to a great loss of hair, leaving only short stumps. Dermatitis may result from the primary irritant effect of the substances used to soften the hair (alkalis and thioglycolate); or allergic reactions may be set up by them or by the 'setting' agents (resins). Dermatitis from these processes is commoner in the hairdresser (hands) than in the client.

Other Hair Applications. Shampoos, particularly the 'soapless' varieties, may sometimes give rise to allergic contact dermatitis of the face, neck, or scalp; and the hands may also be affected.

Bleaching, if frequently repeated, can make the hair dry and brittle.

Hair fixatives (gums or resins) may produce allergic contact dermatitis.

Hair tonics and lotions (which may contain quinine, tar products, rubefacients, mercury salts and perfumes) can give rise to primary irritative or allergic dermatitis of the scalp and adjacent skin. Such lotions and tonics are commoner causes of dermatitis than are the dyes, doubtless because they are much more widely used.

Brilliantines may cause eczematous reactions, especially about the ears, forehead and neck. Sometimes they produce a more unusual reaction first noticed by one of us (G.G.) in 1944¹ (Fig. 2). The first case was a man of 35 who had a mass of small black comedones extending in plaques over the temples from the tails of the eyebrows to the hair line. The unusual distribution led to the discovery that he had for some time been using a brilliantine which, on analysis, was shown to contain a mineral oil mixed with recuperation oil. The condition therefore, was an oil acne analogous to that seen on the forearms of turners and other metal workers. Such a reaction is, of course, unlikely to occur in peace-time when adulterated cosmetics are rarely sold.

Lipstick. Allergic contact dermatitis (cheilitis) may be produced by certain constituents of lipsticks. There is first an itch and oedema of the lips and adjacent skin, later vesiculation, oozing and sometimes bulla formation



Fig. 1. Dermatitis from hair dye, paraphenylenediamine.
Fig. 2. Oil acne from brilliantine.

application of the dye. Then appear erythema, oedema and vesiculation to give the picture of eczema. The lesions often begin first on the upper part of the ear, in the retro-auricular furrow or on the nape of the neck; sometimes the eyelids are affected first, and eventually there is spread over the scalp, brow and face (Fig. 1). There is usually a great exudation and the hair is matted with honey-coloured crusts. The eczematous eruption may spread even further over the shoulders or beyond and lasts at least 10-14 days. Milder attacks with only pruritus and erythema are sometimes seen. Severe conjunctivitis, and even corneal ulceration, may be associated. The hands are often affected.

The oozing lesions may be treated with the following lotion (Milian's):

Methyl green	0.1 gm.
Methyl violet	0.1 gm.
Alcohol, 90%	100.0 gm.

to minimize the risk of secondary infection, and later with a zinc cream.

Applications containing sulphonamides or local anaesthetics must never be used because cross-sensitization is so common. Oral sulphonamides and injected local anaesthetics may also produce reactions in a person who has been sensitized to paraphenylenediamine.

Cold Permanent Waving. Accidents from cold waving processes are, considering the vast numbers involved,



Fig. 3. Cheilitis from lip stick.
Fig. 4. Positive patch test with lip stick. Same patient as in Fig. 3.

and deep cracking (Figs. 3 and 4). Signs and symptoms disappear rapidly on discontinuing the use of the lipstick. The colouring matter is usually the responsible agent, and it may be eosin, dibromfluorescein or, more rarely, rhodamine B. The dye may act directly or, as suggested by Audry and Valdiguié,² it may be that eosin and its derivatives act as photosensitizers. Accidents have been reported

as occurring more frequently in spring and summer. Patients who are allergic to eosin may be able to use, instead, a lipstick coloured with carmine. In certain cases the allergen is the perfume or the excipient of the lipstick.

Creams and Powders. All the creams, powders, rouges, eye-shadows and powder bases can elicit an eczematous dermatitis of the face, but the incidence of such accidents is relatively low. Creams are more liable to produce reactions than are powders. More interesting is the part powders and creams may play in the appearance of facial pigmentations. Some authors³ consider them the most important factor in the pathogenesis of melanosis. We think this is more likely in the case of the *caf²-au-lait* melanoses (analogous to chloasma) than in the typical melanoses of Riehl (brown or violet colour and areolar distribution) which were so frequently seen in France during the war years. In the latter cases local applications may act as photosensitizers, but this does not diminish the importance of other factors, notably endocrine imbalance and dietetic deficiency, in the pathogenesis of facial melanosis.



Fig. 5. Pigmentation from perfume.

Perfumes. The role of certain cosmetics, the perfumed essences, in the production of pigmentation of the face and neck is undisputed. The pigmentation is in irregular patches and tracks where the liquid has been applied and run on the forehead, cheeks, neck and behind the ears (Fig. 5). These perfumes or *eau de cologne* containing certain essences, such as bergamot, are photosensitizing

agents and exposure to sunlight after their use can produce this pigmentation which fades very slowly. The perfumes can also give rise to the more usual oedematous or eczematous eruptions.

Nail Preparations. Alkaline cuticle removers can cause primary irritation of the skin and may destroy the nail. Liquid nail varnish and varnish removers, which contain acetone, can cause the nails to become dry and brittle.

Nail varnish is one of the commonest causes of allergic contact dermatitis due to cosmetics. The skin around the nails is, unexpectedly, very seldom affected and the lesions are found at a distance in areas accessible to the fingers, e.g. face, eyelids, neck, chest, axillae, arms, vulva and perineum, in that order of frequency. The eruption is sometimes eczematous, sometimes dry and scaly. It clears up with the simplest treatment after removal of the cause. The resins rather than the dyes seem to be the allergens.

The unusual distribution of the lesions makes diagnosis difficult for the uninitiated. Relapse sometimes occurs after apparent removal of the cause, and the reason may be difficult to find; some trace of varnish may remain in gloves or shoes, or varnish may have been used to stop a run in a stocking. In one interesting case the cause of relapse was traced to the patient's masseuse who had been given the unwanted varnish.

Deodorants and Perspiration Inhibitors. Dermatitis, both allergic and primary irritative, can follow the use of these products, whether powder, cream or liquid. The factors may be the excipient in creams, perfume, benzoic acid or hexamethylene tetramine (in deodorants), or aluminium salts (the commonest of the perspiration inhibitors). The eruption, usually in the axillae, may take the form of an eczema or of a folliculitis. It may have to be distinguished, by patch testing, from a reaction caused by rubber dress shields or by dye in clothing.

Depilatories. Severe dermatitis due to primary irritation often follows the use of depilatories containing alkaline sulphides. Alkaline calcium thioglycolate is used in some depilatories and seems to be less liable to produce dermatitis than the sulphides. The face and legs are sites of election.

The foregoing are the common causes of dermatitis from cosmetics, but the list could be greatly prolonged by going further into detail, e.g. dermatitis has been reported from the use of hand creams, sun-tan lotions, sun-protective lotions, rubber sponges used to apply cosmetics, etc. Again, the bearer of the cosmetic need not be the sufferer. There are reports of cases where husbands became sensitive to cosmetics used by their wives.

DIAGNOSIS

The diagnosis of dermatitis due to cosmetics is not always as simple as would be imagined, especially when it is in a chronic state or complicated by dermatitis medicamentosa. Careful history-taking is of the greatest importance, and the following general points may assist in arriving at a conclusion.

1. The dermatitis must have begun after the suspected substance was first used.
2. The eruption first appeared at the site of application of the cosmetic; the great exception is, of course, with nail varnish.
3. In the majority of cases the eruption is confined to the area of application of the cosmetic; but wide-spread eruptions can occur.



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4. The signs are those of a contact dermatitis.
5. Improvement follows the discarding of the suspect, and recurrence follows its subsequent use.
6. Patch tests.

Patch tests with the suspected substances can often be of the greatest value. The aim of such tests is to reproduce the disease in miniature. The substance is applied to the skin on a piece of 4-ply gauze 1 cm. square (in the case of powders the gauze can be moistened with water or axillary sweat). Over the gauze is placed a square of cellophane 2 cm. square and the whole is sealed to the skin with a square of elastoplast large enough to ensure that it will stay fast. Test patches must be applied to normal skin near the affected area. In the case of cosmetics the patch will be left in contact for 48 hours unless the patient feels that a reaction is taking place, when it will be inspected earlier. In a positive reaction there may be seen varying degrees and combinations of erythema, oedema, vesiculation, oozing and crusting. While the patch tests are in contact with the skin there may be a flare-up of the dermatitis. This may occur even when there is no reaction on the tested skin, and can be interpreted as presumptive evidence of positivity. Occasionally one sees a delayed positive reaction when eczematous changes appear in the tested area a few days after removal of the patches. A negative patch test cannot be accepted as proof that a suspect can be ignored, and re-testing at a later date may give a different result. In cases where the history does not give a very clear suggestion as to the substance or substances involved it is wise to test with all the cosmetics and soaps recently used (sometimes a formidable undertaking).

TREATMENT

The essential is to find the cause and remove it. In the stage of investigation all cosmetics, suspect or not, must

be removed, and only bland applications containing no possible allergens used. Calamine lotion or liniment or zinc cream are generally safe. Soap should not be used for cleansing. If patch tests are not to be performed the patient should begin again, after the skin has returned to normal, to use the cosmetics one by one for a few days at a time as a practical test for sensitivity. In the majority of cases the sensitivity is permanent and the substance containing the allergen cannot subsequently be used.

Local applications containing sulphonamides or local anaesthetics should never be used because of the danger of cross sensitivity; and penicillin or antiseptic ointments are to be avoided, even if there is secondary infection, for fear of producing yet another sensitization. If a resistant secondary infection should arise, Aureomycin ointment, 3%, is probably the safest application. Anti-histaminics by mouth may be tried, but ointments containing them are not to be recommended as even they may act as sensitizing agents.

Sensitive individuals may be able to use one of the hypo-allergic cosmetics now available, but they should either be patch-tested first or advised to make a cautious practical test.

SUMMARY

The role of cosmetics as causes of dermatoses and the methods of investigating such cases are discussed. Attention is drawn to the danger of producing a secondary dermatitis medicamentosa by improper treatment.

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PORPHYRIA

P. W. J. KEET, M.B., M.R.C.P. (EDIN.)

Cape Town

Porphyria is a rare disease characterized by the passage of excessive quantities of porphyrin in the urine.

Two main types are described:

- (a) Congenital or photosensitive porphyria.
- (b) Acute idiopathic porphyria.

The first reference to this condition was made more than 50 years ago by Gunther. He regarded it as a constitutional anomaly of pigment metabolism, which he named haematoporphyria.

In 1924 Fischer proved that haematoporphyria is a laboratory product and is never naturally excreted—the excreted porphyrins being uro- and coproporphyrin.

In health minimal quantities of porphyrins in the form of coproporphyrin are voided in the urine and faeces. Larger quantities of coproporphyrin are excreted in certain diseases, viz. pernicious anaemia, in alcoholism and also in poisoning by benzene-ring compounds, sulphonamides, lead, selenium and arsenic. Increased excretion under these conditions is called symptomatic or secondary

coproporphyrinuria. The increase, however, seldom exceeds 50 times the normal daily output. In porphyria the urinary excretion is much higher and may reach 80-100 mg. per day.¹

Porphyria may also be induced in susceptible individuals by the administration of chemical products, notably Sulphonal and probably also Trional and Veronal. Any of these may act as a precipitating factor in the person who has the metabolic disorder.²

Incidence. Fewer cases of acute porphyria are recorded in British than in Scandinavian or American medical literature. Barnes has lately shown that porphyria is not uncommon in South Africa.

The congenital type is exceedingly rare and occurs twice as frequently in males, whereas the ratio is approximately reversed in acute porphyria.

Congenital porphyria appears in infancy or early childhood. Acute porphyria develops in the third and fourth decade and seldom before puberty. Rothman,³ however, recorded a case of the first attack of acute idiopathic porphyria in a child of 3 years.

Porphyria is not confined to the human species. Rimington⁴ and Fourie⁵ have described the condition in animals as well.

Etiology. Porphyria is classified as a metabolic disorder—as one of the inborn errors of metabolism.⁶

Photosensitive porphyria occurring, as it often does, in infancy and even in foetal life, has always been accepted as a congenital and familial disease. The anomaly is explained by the inheritance of a gene possessing recessive characters.

Acute porphyria was formerly regarded as an acquired disease, but the frequent familial incidence has altered this conception. Its inheritance is by a gene possessing dominant characters (Gales).

The etiology is still obscure. Turner⁷ is of opinion that porphyria may be the persistence of a foetal pyrrol metabolism. He refers to the great activity of the erythropoietic system in the formation of haemoglobin and suggests that it is there that the evidence for cellular porphyrinogenesis must be sought.

Best and Taylor⁸ and Garrod have drawn attention to the fact that there is no associated increase in the output of porphyrins in abnormal destruction of red cells, nor is there evidence of haemolysis in porphyria. It is thought rather that the disease results from an over-production of porphyrins during haemoglobin synthesis—a reversion to an embryonic or primitive type of pigment metabolism. Garrod regarded porphyrinuria as a liver disorder. Dobriner and Rhoads⁹ remark that the urinary:faecal ratio of porphyrin excretion can be regarded as a very sensitive indication of liver dysfunction.

It has been noted by Brunsting and Mason¹⁰ that alcoholism with liver disorder may evoke an acute attack in latent porphyria.

Although the disorder seems to be linked with excess of porphyrin, it is not clear whether such excess *per se* is the only factor. There is no clarity either as to the degree of excess which is necessary to precipitate an attack, because, even in the latent phase, high concentrations of porphyrin may be present. Experimental evidence seems to involve porphyrin as a cause. Nesbitt, quoting Leitner, states that porphyrin injected locally or intravenously interrupts the normal rhythmic contractions of the bowel, with the occurrence of spasm and atony in the same portion of the intestinal tract. Thorner¹¹ reports a case of multiple neuritis in a female, following weekly injections of haematoporphyrin, as treatment for a psychotic disorder. The symptoms disappeared when the drug was discontinued. Kooy¹² regards porphyrin polyneuritis as belonging to the toxic polyneuritides.

Halpern and Cosey¹³ observe that some of the familial cases of porphyria may be asymptomatic, but that in these, acute attacks may be induced by barbiturates. Scobey¹⁴ points out that barbiturates are hypnotic derivatives of urea and that poisoning from the use of barbiturates results from their conversion into hydrocyanic acid derivatives. He quotes Fearson that cyanic acid is formed by the hydrolysis of urea by urease.

Source of Porphyrins. Haemoglobin is a complex made up of a pigment of the pyrrol group—known as protoporphyrin—and combined with iron and a protein—globin.

Porphyrins are widely encountered in plant and animal life, from the highest to the lowest forms. A porphyrin is the pigment basis of chlorophyll. Coproporphyrin is formed in the intestine from bilirubin. Uroporphyrin is normally found in small quantities in the urine. According to Best and Taylor *et alii*, under normal conditions, neither of these is formed from the breakdown of haemoglobin, but from porphyrins contained in the food. Shemin and Rittenberg¹⁵ suggest that glycine of dietary origin is utilized by the body for the synthesis of porphyrin. An Editorial¹⁶ refers to Hans Fischer's findings¹⁷ that porphyrins may be built up *in vitro* from simple compounds, such as amino-acetic acid. By using isotope tracer technique the experimenter demonstrated the participation of amino-acetic acid in the synthesis of porphyrin in the human subject also.

Classification of Porphyria. Waldenstrom, Gray *et al.*¹⁸ proposed the following classification:

I. Photosensitive porphyria.*

* Sato and Takahashi²⁸ describe a fatal type of congenital porphyrinuria, named by them megalosplenica congenita, with onset at birth, photosensitivity, enlarged spleen, hypochromic anaemia and a strong familial incidence.

(a) Congenital, characterized by porphyrinuria and skin lesions, appearing in early life.

(b) Delayed cutaneous porphyria, appearing in later life.

II. (1) Acute toxic porphyria.

(2) Acute idiopathic porphyria, a chronic disorder of the pyrrol metabolism with acute episodes and latent between attacks.¹⁹

(a) Latent, with excretion of uroporphyrin, without other clinical signs of porphyria (found in relations of patients afflicted with the disorder).

(b) The abdominal form, with visceral manifestations.

(c) The nervous form, with paralysis.

(d) The classical form, with abdominal and nervous manifestations.

(e) The comatose form.

In I and II uroporphyrin is mainly excreted.

III. A group excreting coproporphyrin with intermittent abdominal pain.²⁰⁻²²

Linder²³ draws attention to the fact that acute idiopathic porphyria arises spontaneously, whereas acute toxic porphyria is precipitated by certain drugs and can be established when a causative agent is found.

Petrie²⁴ observes that latent porphyria can only be detected by examination of the excreta.

Morbidity Anatomy. In congenital porphyria the skin lesions occur in the areas which are exposed to light. Early lesions are vesicular or bullous (hydra aestivale). Frequent blistering with added infection produces pitting and scarring and causes mutilation of ears, eyelids, nose, nails and digits. Erythrodontia or red staining of deciduous teeth may appear from excessive formation of uroporphyrin during foetal life. Red staining may also be found in permanent teeth and bones.

In acute porphyria the main incidence is on the nerve tissue and muscles. Lesions have been found in the central, peripheral and autonomic nervous system. Nuclear vacuolation and chromatolysis in anterior horn cells and sympathetic ganglia may appear. An outstanding feature is a patchy degeneration of the myelin sheath. Halpern and Cosey mention nerve cell degeneration in cerebral cortex, basal ganglia, cerebellum and spinal cord. Denny Brown and Sciarra²⁶ claim that primary damage to the nervous system is not a degeneration but an impairment of the myelin, comparable with a widespread, patchy and intermittent ischaemia, similar to that which results from pressure on a nerve. The ischaemia follows an angiospasm. This is substantiated by the frequent finding of narrowed retinal arteries and is also suggested by the occurrence in some cases of anginal attacks.

In the liver central necrosis is often found and in the kidney degenerative changes in the glomeruli and cloudy swelling with atrophy of the tubular epithelium, have been observed. Muscle fibres may lose their striation and staining properties with partial disappearance of the sarcolemma.²⁷ Hyperblastic bone marrow changes have been described.

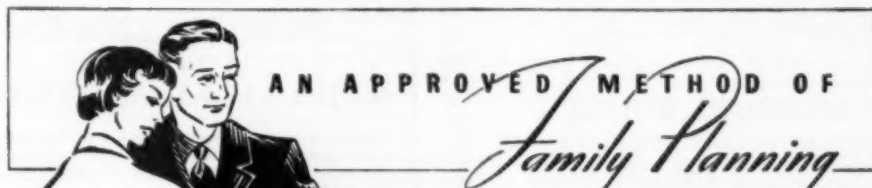
Symptomatology. In congenital porphyria, as already stated, various skin lesions are found.

(a) Hydra aestivale, characterized by small bullae on exposed parts. (These are by no means found only in porphyria.)

(b) Eczema solare and, more rarely, epidermolysis bullosa.

Erythrodontia has been referred to. Occasionally hirsutism of male distribution in females is mentioned.

Acute porphyria may be preceded by certain prodromal symptoms: weakness, lassitude, anorexia, loss of weight, constipation, nervousness, mild hysteria and depression. As Nesbitt points out, acute porphyria is in most cases a chronic disorder with recurrent episodes and remissions over periods ranging from months to many years. For this reason Watson²⁸ prefers the designation 'acute intermittent porphyria'. Abdominal pain is the most constant finding. The pain is colicky and may range from a severe discomfort, as in spastic colon, to extreme agony. Our patient had such violent paroxysms of pain as to cause him to writhe and at times assume an opisthotonos



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posture. The pain may be generalized or located over gall bladder region, back or pelvic basin. It may resemble that of renal colic. In other cases there may be praecordial pain, or the pain may appear in the lower limbs. In rare cases pain may be absent (Pohl and Roberts). Vomiting is a common accompanying feature of abdominal pain. Palpation usually reveals no local tenderness, nor is it resented. The abdomen is soft. It may be distended and silent, or only the heart sounds may be heard on auscultation. Constipation is almost a constant accompaniment of the disorder. During the acute attack it may be impossible to relieve the patient by purgation or enemata. There is inability to pass flatus. Diarrhoea has been recorded occasionally. There may be incontinence of faeces.

Nervous manifestations are mainly those of loss of motor function and sensory impairment is not often noted. An early sign is muscular weakness, which is usually followed by a lower neurone paralysis—partial or complete.²⁹ Recovery may be rapid in milder attacks. Extreme flaccid paralysis is of grave significance. Waldenstrom and others observe that Landry's ascending type of paralysis, although recorded, is of very rare occurrence. The deep reflexes may be exaggerated at the onset of the attack and later on become sluggish or unequal or completely disappear. Cranial nerve involvement is manifested by dysphagia, dysphonia, diplopia, facial palsy and respiratory failure from bulbar palsy. The pupils may be unequal, irresponsive to light, dilated or contracted. Convulsions and coma may appear.

Psychological Symptoms. Most patients exhibit one or other aberration during the acute episode: delirium, disorientation, hallucinatory or delusory states with confabulation of the Korsakoff type, or psychic disorders of the manic-depressive or schizophrenic type, were encountered. Hysterical outbursts, querulousness, irritability and other personality changes often appear when the abdominal symptoms lessen. Suicide is a possibility.

Tachycardia and hypertension are almost invariable findings during the acute episode. Hypertension is ascribed to vascular spasm leading to wide-spread intermittent ischaemia. The effects of this may be stated briefly:

Arterial spasm—*ischaemia* of retina: amblyopia.

Arterial spasm—*ischaemia* of heart muscle: praecordial pain.

Arterial spasm—*ischaemia* of nerve tissue: paralysis, convulsions, coma.

With the remission of symptoms the pulse rate becomes normal and hypotension may be found. In a few patients an icteric tinge or well-developed jaundice was observed.

Photosensitivity is mentioned in a small percentage of cases and as Brunsting and Mason point out, the photodynamic mechanism of this process is obscure. A case with photosensitivity and scarring is mentioned by Nesbitt and Watkins.³⁰ Barnes, in his series, refers to 2 cases with bullous eruptions on hands, with slow healing and scarring; and another with mutilation of finger and toe nails, who had developed facial hirsutism.

Spasm of the retinal arteries with amblyopia may present during the acute phase. Sometimes the patient remembers the passage of blood or dark urine. Dark colouration of the urine is, however, a late development

and may appear as late as 48 hours after being voided. Exposure to sunlight or acidification usually effects the change to a burgundy-red or dark colour. Some patients complain of dysuria or retention. Albumin may appear. Pigmentation of the skin has been reported by Pohl and Roberts, Nesbitt, Barnes and others, but it is an unusual finding.

The temperature may be moderately raised from the commencement. If the temperature appears later, pneumonia (a frequent complication) should be suspected.

Menstrual Disturbances. Dysmenorrhoea or amenorrhoea may occur. *Characteristic anaemia* or changes in the cellular elements of blood or bone marrow are absent in acute porphyria (Barnes).

Biochemical and Other Findings. Porphobilinogen—a colourless chromagen in the urine of porphyriurias, and first described by Waldenstrom, is considered to be pathognomonic of acute porphyria. Porphobilinogen is demonstrated by Ehrlich's benzaldehyde reaction. It must be remembered that other pigments, viz. indole, leucin, tyrosine, cystin, skatol and urofaecins, may also darken the urine.

It has generally been accepted in the past that uroporphyrin III was the predominating isomer in acute porphyria. The findings of Grinstein, Schwartz and Watson³¹ and afterwards those of Prunty³² have cast a doubt upon the existence of uroporphyrin III.

Wassermann and flocculation tests are negative.

Blood urea ranges from 20-80 mg. per 100 c.c.

The A:G ratio is often reversed.

(In cases of diabetic polyneuritis, Sterling, Silver and Ricketts³³ recommend that urinary porphyrins be estimated.)

Glucose tolerance was found to be reduced by Pohl and Roberts.

Linder, Nesbitt, Roth and Golden record gross depletion of serum chlorides.

The blood sedimentation rate is often raised during the acute attack. A leucocytosis is very common.

The B.M.R. varies. Some muscles show a reaction of degeneration. The EGG may record low voltage waves—diphase or inverted T waves in lead II, or a raised ST segment. X-ray of the gastro-intestinal tract may show areas of spasm and distension with numerous fluid levels.

Tests for Porphyrins. Identification depends on their clinical isolation as methylesters and their presence may be inferred spectroscopically and by fluorescence tests. Melting point estimation of methyl-esters is also made to distinguish between various isomers.

The zinc metal complex of uroporphyrin, which occurs in acute porphyria,³⁴ may be differentiated spectroscopically.

Maebling³⁵ states that increased yields of urinary porphyrin can be obtained by hydrolysis with hydrochloric acid.

Prognosis. This is good in the congenital type.

In acute porphyria where nervous manifestations are found the mortality is very high. Approximately 80% die within 5 years.

Respiratory failure and pneumonia are mainly responsible.

In cases where only abdominal symptoms present, the outlook is more favourable.

Diagnosis. The finding of dark-coloured urine with an excess of porphyrin is diagnostic. The appearance of otherwise unexplained acute abdominal pain, tachycardia and neuro-muscular symptoms, demands a search for porphyrin and porphobilinogen.

Differential Diagnosis. Porphyrin should be considered in obscure nervous disturbances, particularly hysteria, unexplained peripheral neuritis and flaccid paralysis, when accompanied by abdominal pain. In Sweden cases of neurasthenia are examined for porphyrin (Scobey).

Locomotor ataxia may be suggested by abdominal pain, loss of reflexes and fixed pupils. The presence of sensory loss and a positive Wassermann reaction exclude porphyrin.

Hysteria can be excluded by the marked tachycardia, unequal reflexes and porphyrinuria.

Progressive muscular atrophy is differentiated by the absence of pain, slow onset with fibrillary tremor and progressive course.

Anterior poliomyelitis may resemble porphyrin closely. The epidemic character of the former and onset in early life, asymmetrical paralysis, fever and frequent stiff neck, are differentiating features.

Peripheral neuritis is suggested by the presence of marked sensory and motor loss commencing in the extremities and muscle tenderness.

Arsenical neuritis presents motor and sensory features, hyperkeratosis, skin lesions and the presence of abnormal amounts of As in the urine.

Lead palsy offers a few features resembling porphyrin, viz. colic and constipation, but the palsy affects mainly the extensors of forearm and hand with wrist-drop. It rarely occurs in the lower limbs and when it does, the extensor muscles of the toes are involved. The urine may contain a marked increase of porphyrin but no porphobilinogen.

Guillain-Barré's syndrome can be differentiated from the nervous manifestations of porphyrin by motor nerve involvement in the latter, with a poor prognosis and motor and sensory involvement in the former, with a good outlook (Peters, quoting Yeager).

Congenital porphyrin occurs mostly in males at an early age and symptoms are restricted to skin lesions and porphobilinogen is absent.

Addison's disease may be suggested when pigmentation and hypotension are present, but the absence of pigmentation in the mucous membranes, lack of response to adrenal cortical extract and salt, serves to exclude this condition.

Acute abdominal conditions can be dismissed by the absence of boarding or rebound tenderness. Despite this a number of laparotomies have been performed.

Renal colic may come under consideration when the dark urine is mistaken for blood and the pain is assumed to arise from stone in the kidney or ureter.

Gallstone colic or biliary dyskinesia may be diagnosed when the pain is referred to right hypochondrium; and rapid pulse with abdominal pain may suggest a ruptured tubal pregnancy.

Hypertension with albuminuria, oliguria and dark urine may suggest acute glomerular nephritis.

Treatment. In congenital porphyrin protection from sunlight is necessary.

In intermittent porphyrin various methods have been advocated but no specific has yet been found to prevent or abort an attack.

Calcium is stated to form insoluble salts with the porphyrins and Ca intravenously has been reported to be beneficial.

Kaolin is also recommended as *in vitro* experiments show absorption of porphyrin.

Adrenal cortical extract and salt have been tried, but their value is not convincing.

Neostigmine may cause relief in some, but is not recommended.³⁶

Barnes draws attention to the use of intravenous fluid therapy as a means of arresting the progress of the attack. This seems theoretically sound, as such treatment is indicated to remedy dehydration from vomiting and it serves to 'dilute' the porphyrins and supplies nourishment.

Anti-cirrhotic treatment has been found to improve cases of alcoholism with liver dysfunction (Brunsting and Mason).

Bowel washouts are without result.³⁷

Pethidine is useful as an antispasmodic and analgesic.

Barbiturates should not be given as a sedative or hypnotic.

For respiratory embarrassment a respirator is indicated.

Massage and passive movements should be applied early for the wasting and splinting.

Porphyrinurics should be warned against alcohol in excess.

Barbiturates and other drugs with precipitating tendencies should be avoided.

CASE REPORT

On 5 July 1951 a D/Sgt. of Police, *aet.* 36, was admitted to hospital complaining of intense abdominal pain, vomiting and obstipation. I was asked to see him to decide whether or not he was a surgical emergency.

History. He stated that the first symptoms appeared 10 days before when he commenced having a severe attack of cramp-like pain in the abdomen, intermittent and at times associated with nausea and vomiting. On 4 July 1951 his pain recurred with such intensity that he called in the District Surgeon, who gave him some medicine. The next day the District Surgeon on finding that he was not relieved, sent him to hospital. He volunteered the information that in 1943, while on service in Egypt, he had attacks of a similar kind. He reported sick and was sent to hospital but the M.O. was not impressed by his story and discharged him after 2 days. He became weak and had no appetite and at times had difficulty in passing urine. On questioning he stated that his urine was sometime dark.

On Examination. The patient had a good colour, a pulse of 140 per minute and a blood pressure of 174/102 mm. Hg., temperature normal and tongue thickly coated. He appeared to be in great pain and was restless. At times the pain was so intense that he lay in the opisthotonos position. The abdomen moved with respiration, was not markedly distended and there was no visible peristalsis. Abdomen felt soft and no tenderness was elicited. There was no rebound tenderness, no lumps were felt and the rectum was empty. On percussion the note was resonant and the liver dulness not impaired.

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On auscultation no bowel sounds were noted and the heart sounds were widely transmitted. Chest and heart: nothing abnormal was detected, and except for markedly exaggerated reflexes and sluggish pupil-reflexes, nothing of note was found in the central nervous system.

I decided that there was no need to summon the surgeon and ordered pethidine and belladonna and asked the House-man to send up the urine for porphyrin examination and the stomach contents for strychnine. These examinations were done the next day and both findings were negative. The urine was sent up again and on 11 July porphobilinogen + and urobilin + were found, the blood urea was 84 mg. per 100 c.c. and the urine had a brick-red colour.

He was given calcium gluconate intravenously from this time.

X-ray examination of the abdomen revealed no signs of obstruction but only gaseous distension.

He was comfortable until 18 July, when after lying with his leg uncovered in the sun for 1½ hours, he had so severe an attack of pain as to cause him to cry out. The next day he was confused and disorientated. The reflexes became sluggish and voluntary power in arms and legs was markedly reduced. He showed coarse tremor on voluntary movement. There was some sensory impairment. Blood pressure, 140/85 mm. Hg.

4 August. Temperature, 102° F. Respirations, 40 per minute. Pulse, 140 per minute. There were signs of bronchopneumonia and he was ordered Penicillin, which relieved him in 3 days when his temperature became normal.

11 August. Weakness of respiratory muscles caused embarrassment of breathing and he was placed in the iron lung for 2 days.

20 August. Mentally clear and answered questions intelligently. There was generalized wasting of muscles of arms with paralysis and wrist and foot drop, he could only flex fingers and toes. Could not feed himself. Could move head freely, bend knees, adduct and abduct thighs.

Reflexes. Knee jerks sluggish; ankle jerks present. Slight cremasteric reflex, left side. Biceps and supinator jerks, absent; triceps jerks, weak. Abdominal reflexes absent and plantar reflex flexor. Sensory loss to light touch and pin-prick generalized in the arms and below D 10-12 on abdomen and below L3 in legs. Passive movement and position and stereognostic sense normal. Cranial nerves normal. Retinal arteries somewhat spastic.

From 3 to 12 September he had diarrhoea. After this his condition commenced to improve and he was able to get up. Massage and passive movements were started as early as possible and cock-up splints were applied to correct the wrist drop. He gradually developed enough strength to be able to walk unaided and can now feed himself. He was discharged as an out-patient on 31 January 1952, but will continue to attend for physiotherapy. It is possible that dorsiflexion of wrists and fingers will always be somewhat impaired.

Special Examinations.

ECG. Flattened T wave, lead I.

Inversion of T waves leads II, III, and aVF.

Q waves of 2 mm. in lead II.

QRS, 0.1 second. Sinus tachycardia, 126 per minute. Heart in vertical position.

Red cells ranged from 4 to 4.5 millions per c.mm.

Leucocytes ranged from 16,800 to 7,200 per c.mm.

Differential counts showed no departure from normal.

Blood urea ranged from 84 mg. to 32 mg. per 100 c.c.

6 July 1951:

Alkali reserve reduced to 30 vols. CO₂ %.

Urinary diastase, 32 units.

Haemoglobin, 13.85 gm. %.

Porphobilinogen negative.

Acetone positive.

Chlorides as NaCl, 200 mg. per 100 c.c. (vomiting stage).

Stools—no amoebae, cysts or ova (10 July 1951).

Porphobilinogen, positive (11 July 1951 and 11 August 1951).

Coproporphyrin of undetermined isomer found on 17 July 1951.

Wassermann reaction, negative. Colloidal gold, 0 (25 July 1951).

Cerebrospinal fluid normal (25 July 1951).

B.M.R., -29% (31 July 1951).

20 August 1951:

Non-protein nitrogen, 72 mg. per 100 c.c.

Serum protein, 5.82 gm. %.

Albumin, 3.81 gm. %.

Globulin, 2.01 gm. %.

Serum Ca, 10.1 mg. per 100 c.c.

Blood glucose, 150 mg. per 100 c.c.

Blood cholesterol, 105 mg. per 100 c.c.

SUMMARY

1. The subject of porphyria is discussed in its general aspects and acute porphyria in more detail.

2. A case of acute porphyria is reported which seems to fall under the rarer category of type III in the classification.

3. Reference is made to the not infrequent decision to regard the abdominal signs as indication for laparotomy.²² Waldenstrom mentions 29 cases in which laparotomy was performed.

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ASSOCIATION NEWS : VERENIGINGSNUUS

GRIQUALAND WEST BRANCH: MEETING HELD ON 8 MAY 1952

AT THE SCHOOL FOR THE PHYSICALLY HANDICAPPED, DISKOBOLUS

Present. Dr. S. Perel in the Chair, 19 members and Sunday staff of the School. Dr. Perel stated that to-night was the first visit many of the members had made to this Institution and he hoped that this would be the first of many.

Dr. Vaughan, the Principal of the School, who until recently was the Vice-Principal of the Worcester School for the Blind and is at present occupied in the attempt to get the Native languages together and read in Braille, welcomed the visitors and emphasized the important part that the medical profession and its auxiliaries play in enabling the school to run.

Dr. H. G. Pretorius, the Chief Medical Officer of the School, shortly described the growth of the School, from one doctor to two and then later to include the services of an orthopaedic surgeon and various auxiliaries such as psychotherapists, occupational therapists, teachers, speech therapists, etc. As cases are only accepted if they possess a physical disability, their progress and improvement takes not days, but weeks and months of patient handling in order to build them up physically and psychologically, so that they can take their places as well-adjusted members of the community. The School has now grown to be the largest fully state-controlled institution in the world. He then introduced Dr. Obholzer whom he described as a foremost authority on the question of cerebral palsy.

Dr. Obholzer first paraded about 30 cases of various types of cerebral palsies in various stages and then he discussed the subject. Many of these were once considered irremediable but now have a fair chance of improvement, but only when tackled by a team of teachers and doctors. There are 5 distinct types described, some distinct but many are mixed, and therefore correct diagnosis is most essential, e.g. the School often gets sent cases of post-polio, etc.

1. The *Spastic Group*—characterized by the 'clasp knife' phenomenon.

2. The *Flaccid Group*.

3. The *Athetotic Group*—where the basal ganglia are chiefly affected.

4. The *Rigidity Group*—characterized by the 'lead pipe' phenomenon.

5. The *Tremor Group*.

6. The *Ataxic Group*.

All these types were demonstrated and it struck one how unembarrassed and matter-of-fact the young patients were.

He stressed that the aim of treatment was to provide physiotherapy and medical care, supply the educational needs, and vocational training and to rehabilitate the patient as a whole being and also to rehabilitate the family.

(Tea was taken at this stage.)

After the refreshments, Dr. Hofmeyr proceeded to demonstrate cases. Though a wide variety could be shown, he confined himself to real rarities which he thought might be of especial interest.

1. One of the first *hemispherectomy* cases ever performed: The patient, a forceps delivery, later developed epilepsy, tantrums and one side of the body was poorly developed. On the basis of a diagnosis of a porencephalic cyst, Dr. Krynauf and his team removed the entire hemisphere leaving only the basal nuclei intact. She walks quite well now and has a sweet disposition.

2. A case of *cerebellectomy* for presumably cerebellar cysts—also performed by Dr. Krynauf; though ataxia is still marked, the patient is improving under therapy.

3. A case of *hydrotic cysts* in the cerebral cortex. Though an upper motor neurone defect is left, the patient is improving so well that it is hoped that he will be able to return to his teaching profession.

4. A typical case of *fragilitas ossium* with 13 fractures at various times and typical blue sclerotics. The differentiation from *osteogenesis imperfecta* was stressed.

5. A *Pocket Hercules* was shown but the typical weakness of pseudohypertrophic muscular dystrophy clearly demonstrated.

6. A different, not clearly differentiated, type of *muscular dystrophy* where extensive muscular atrophy was present, was the final case.

After the Chairman had thanked Dr. Pretorius and his staff for a most interesting and instructive evening, the meeting was closed.

PASSING EVENTS

VAN RIEBEEK NUMBER OF THE JOURNAL

A limited number of copies of the van Riebeeck number of the *Journal* is still available to members of the Association, at the reduced price of 2s. per copy.

Orders accompanied by a remittance should be sent in as soon as possible, as there has been a considerable demand for this issue.

Dr. F. P. Reid of Johannesburg will be away overseas from 1 July to 14 September 1952.

Dr. Sydney Friedman, M.B., Ch.B., D.P.M., has commenced private practice as a Specialist in Psychiatry and Neurology at 417-B Cavendish Chambers, Jeppe Street, Johannesburg.

Telephones:—Rooms: 23-7223; Residence: 45-3661.

Dr. M. Jordaan, Thoracic Surgeon, is now residing at *Naidaus*, Eyton Road, Claremont, C.P. His residence telephone number is 7-7385.

Dr. P. Leftwich of Cape Town has changed his residential telephone number to 7-4403.

Dr. M. Schaffer has returned from a post-graduate visit overseas. Whilst overseas, Dr. Schaffer was admitted as a Fellow of the Royal College of Surgeons (Edinburgh). He intends to resume practice in Durban with his partners, Drs. N. Smith and J. Friedlander.

Dr. M. M. Suzman of Johannesburg has been appointed a Corresponding Editor of the recently established *Journal of Clinical Nutrition*, published in Philadelphia.

The *Journal of Clinical Nutrition* is the only periodical devoted to the practical application of our newer knowledge of nutrition. It will be aimed at the specialist as well as the family physician and will contain original articles stressing the clinical aspects of nutrition, review and summary articles, and a large co-ordinated abstract section.

SOUTH AFRICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE: ANNUAL MEETING 7-12 JULY 1952

Members of the Medical Association are cordially invited to attend the meetings of the South African Association for the

Advancement of Science, to be held at the University of Cape Town, Rondebosch, C.P., from 7-12 July 1952.

Those who are not members but who wish to participate in excursions and functions should, however, apply for Associate Membership for the duration of the Annual Meeting. Write to the Chief Recorder, South African Association for the Advancement of Science, Archaeological Survey, University of the Witwatersrand, Milner Park, Johannesburg.

INTERNATIONAL CONGRESS ON DIABETES

The First International Congress of the International Diabetes Federation will be held in Leyden, Holland, from 7-12 July 1952.

Those interested in attending should communicate with the Secretary-Treasurer, Dr. F. Gerritzen, 33 Prinsegracht, The Hague, Netherlands.

CORRESPONDENCE

CYST-HEPATIC DUCT

To the Editor: On 22 December 1951 (this *Journal*, p. 942), Dr. C. R. MacPherson published an article *Congenital Hypoplasia of the Gall Bladder with Cyst-Hepatic Duct* in which he formulated a theory to account for the origin of cyst-hepatic ducts on the grounds of developmental anomaly rather than on those of atavistic reversion. I would like to comment on both concepts.

I cannot conceive how the theory of atavistic reversion in connexion with cyst-hepatic ducts arose in the first instance, because no similar ducts have ever been observed in any of the lower vertebrates or any of the primates studied. One of Dr. MacPherson's referees, Lockhardt (1927), writes of agenesis of the gall bladder as an atavistic reversion as this condition is normally found in some animals, viz. Cetacea, Perissodactyla Ungulata, Hydracoea, and some rodents. Dr. G. W. Bartelmez, of this Department, feels that atavism in agenesis of the gall bladder could be claimed only if primitive groups in the primate line, such as tree shrews, lack a gall bladder.

It is known that the pars cystica (caudal portion) of the hepatic bud (which develops from the hepatic rudiment of the duodenal endoderm) gives rise to the gall bladder and cystic duct, and that the pars hepatica (cephalic portion) of this rudiment divides into a right and left mass which invades the mesenchymal tissue of the septum transversum forming the branching hepatic trabeculae, which subsequently canalize to form the bile capillaries. The single hollow stalk of attachment of the pars hepatica and pars cystica to the duodenum elongates to give rise to the bile duct. Thus the pars hepatica forms the common hepatic duct which branches into right and left hepatic ducts, and these, in turn, form the hepatic trabeculae. Only later are the hepatic ducts canalized, and it should be noted that the hepatic ducts are developed from the solid hepatic stalk and then the trabeculae branch from these. It should also be noted that the hepatic ducts lie, for the main part, within the liver substance.

Dr. MacPherson's sketches seem to ignore the concept of the common hepatic duct dividing into two major ducts, for in the sketches all the trabeculae appear to enter the common hepatic duct. His basic premise is made on this misconception, and he also does not take into consideration the rather simple sequence of events stated above because he postulates that the gall bladder develops as a diverticulum of one of the hepatic trabeculae and then it would appear that one, or more, hepatic ducts (by which I presume he means *trabeculae* or *ductules*) might be drawn out with the elongating gall bladder diverticulum and, depending on how far above the normal position the diverticulum originated one could explain the occurrence of a cyst-hepatic duct at any point from the fundus of the gall bladder to the junction of the cystic and common bile duct. . . . In other words, he almost reverses the normal sequence of events and, anyhow, on his hypothesis the gall bladder should be intra-hepatic.

In criticizing Dr. MacPherson's concepts, I would like to discourage attempts to account for certain anomalies on a theoretical embryological basis. One should only formulate a theory on factual evidence, not on another hypothesis: that is why the above-mentioned pretty sketches would only be valid if they were of actual reconstructions made from serial sections of embryos.

I wish to trespass but briefly on the pathologist's territory when I note, on looking through the literature on this subject, that all these so-called ducts which have been reported are associated with one or other form of chronic infection partly portrayed as intra-abdominal adhesions. Dr. MacPherson's case also has an overwhelming history of infection and evi-

dence of dense adhesions in the region of the gall bladder. He also found a thrombosed portal vein next to the 'duct' in the liver substance. This has led me to wonder whether these 'ducts' (which incidentally are not reported to have been studied histologically) could not possibly be cords of fibrous tissue containing perhaps a dilated blood vessel.

Ronald Singer.

Carnegie Institution of Washington,
Department of Embryology,
Baltimore,
Maryland, U.S.A.
9 May 1952.

BENIGN GASTRIC ULCERS AND RADIO-ACTIVE IODINE

To the Editor: In your issue of 12 April 1952, p. 301, Drs. Greenwood and Samuel report 2 cases of benign ulcer on the greater curvature of the stomach.

Case 2 had been treated with radio-iodine for hyperthyroidism and 7 weeks later presented herself for a medical examination because she had had a severe haematemesis. The patient was X-rayed 10 weeks after the radio-iodine treatment, when she was found to have a large ulcer on the greater curvature opposite the incisura angularis and also a duodenal ulcer. After 4 weeks of intensive medical treatment an X-ray examination showed complete healing of the duodenal ulcer but incomplete healing of the greater curvature ulcer. In their commentary, Drs. Greenwood and Samuel go on to discuss the possibility that the radio-iodine was responsible for the duodenal and gastric ulcers and for the slow healing of the gastric ulcer; and although they admit that Miss Alper of the Physical Research Laboratories, Pretoria, was of the opinion that the duration of the exposure was insufficient to cause a direct burn of the mucosa, they nevertheless consider that 'a lesser degree of damage predisposing to subsequent peptic digestion cannot be excluded'.

In view of the seriousness of the suggestion that radio-iodine therapy may give rise to ulceration of the stomach, it is considered that it merits some discussion.

Drs. Greenwood and Samuel inadvertently left out the dose of radio-iodine the patient was given. They state the basal metabolic rate was high, but do not give the exact figure. They also state the uptake by the thyroid of the radio-iodine was high, but again do not state how high.

In the absence of this information, particularly what the dose of radio-iodine was, it will have been impossible for any of your readers to form an opinion whether there was, in fact, any relationship between the radio-iodine and the ulceration. I am consequently supplying the following details and comments:

The patient was given only 3.6 millicuries of radio-iodine on 6 December 1950. The B.M.R. had been previously + 20%, and the uptake of a tracer dose on 9 November 1950 was 44%.

Neither Drs. Greenwood and Samuel, nor Miss Alper, knew that the 3.6 m.c. of radio-iodine—a relatively small dose—was given in some 80 to 100 c.c. of water.

One has to consider this under the two headings:

(a) The possibility of chemical irritation, to which Drs. Greenwood and Samuel refer.

(b) The radiation effect from the radio-iodine.

(a) As far as the possibility of chemical irritation is concerned, it must be realized that 4 millicuries of radio-iodine contain an infinitesimal quantity of iodine estimated at only 0.032 of a millionth of a gm. of iodine (2 millicuries of iodine¹²¹ weigh 0.016 micrograms).

Even the most convinced homeopaths would scarcely claim that this infinitesimal quantity of iodine could have a chemical or allergic effect resulting in haematemesis and ulceration.

(b) 3.6 millicuries in a 100 c.c. of water mixed with the contents of the stomach would spread over a considerable area of the stomach. The radiation would not be concentrated at one point. In the absence of pyloric obstruction and, judging from Fig. 5, the stomach was emptying readily, the radio-iodine would have started to pass out of the stomach very soon after ingestion. Moreover, even if it were retained in the stomach it would have been rapidly absorbed.

In animal experiments it has been shown that the radio-iodine can be detected in the thyroid 2-3 minutes after it is put into the stomach through a tube; 50% of the radio-iodine in animals is found in the thyroid within 5 hours. In our own figures when doing the uptake test by the method of Morton, Ottoman and Peterson (*J. Clin. Endocrinol.*, December 1951, Vol. 2, No. 12, p. 1572) we find that the thyroid already contains at 1 hour about 50% of the radio-iodine which it will take up at 24 hours. It depends on the state of activity of the thyroid.

Also, it must be recalled that the radiation from the radio-iodine was spread out over a relatively large area of the stomach, and could not have continued for more than say 1-2 hours, and then in steadily decreasing intensity.

The radiation in roentgen equivalents with a dose of 4 millicuries of radio-iodine to a 50-gm. thyroid, with an uptake of 80%, is 6,000 r. The concentration of iodine in the thyroid is 10,000 times greater than in the blood or in any other organ or tissue. The biological half-life in the thyroid is 6 days, and even at the end of a month, the thyroid still receives a small amount of radiation. The thyroid takes up the radio-iodine and not the fluid in which it is dissolved, yet there is no ulceration in the thyroid as the result of the therapeutic doses of radio-iodine.

From the above figures it will be appreciated that the amount of radiation which any square centimetre of the stomach would have received from the radio-iodine, would have been infinitesimal. It certainly could not have been enough to pre-dispose the mucosa to ulceration.

The following facts must also be taken into consideration: Animal experiments have not shown, even with large quantities of radio-iodine, any damage to the gastric mucous membrane. Thousands of cases have now been reported in the literature who have been treated with ^{131}I for hyperthyroidism as well as for carcinoma of the thyroid, with far larger quantities of radio-iodine, without any side-effects in the stomach.

Three hundred cases of hyperthyroidism, carcinoma of the thyroid and cardiac conditions have now been investigated and/or treated by myself or under my supervision. The cardiac cases and carcinoma of the thyroid cases received 20 millicuries at a time, repeated at intervals of several weeks, and yet we have not noticed at any time any gastric symptoms.

Trunnell and Marinelli (*Journal of Clinical Endocrinology*, 1949, Vol. 9, p. 1138) have given enormous doses for carcinoma of the thyroid, as much as 350 millicuries in a single dose, that is exactly 100 times the amount this patient was given. One of their patients received as much as 906 millicuries in 15 months. Although these heavy doses depressed the haemopoietic system, they did not cause any gastric symptoms. The usual dose of radio-iodine given for hyperthyroidism does not cause any side-effects.

My notes on this patient show that she did not complain of any side-effects after the radio-iodine, and as Drs. Greenwood and Samuel state, the hyperthyroidism greatly improved.

The patient, who was 6 weeks pregnant when given the radio-iodine, did not have any severe symptoms referable to the gastro-intestinal tract, but she had in fact complained of epigastric pain for some time before the radio-iodine was given. Drs. Greenwood and Samuel were, apparently, not given this very relevant information. When first I saw her she appeared pale and anaemic and, six weeks before she had had an intravenous pyelogram with negative results. It is significant that her gastric ulcer had penetrated the pancreas. Pyelography is not a very unusual history because of pain in the back with this type of penetrating ulcer.

Her blood count on 3 November, i.e. a month before she was given the radio-iodine, was: red cells, 3.98 million per c.mm.; haemoglobin, 11.9 gm. %; white cells, 11,800 per c.mm.; colour index, 1.01. She was thus anaemic before the

radio-iodine was given and this was probably due to the gastric and duodenal ulcers.

In the light of all these facts the haematemesis and the gastric and duodenal ulcers can be explained on the history and the clinical grounds without invoking the effect of the radio-iodine. The possibility that there was any relationship between the ulcers and the radio-iodine can be very definitely disregarded.

The suggestion of contra-indications, not based on any sound evidence, does a disservice to a method of treatment, which is now generally accepted as the ideal for hyperthyroidism.

3-5 Dunkeld Chambers,
Smal Street,
Johannesburg.
17 May 1952.

M. Weinbren.

HYSTERECTOMY

To the Editor: Dr. Strasheim is to be congratulated on his excellent article *Post-Menopausal Haematometra* (this *Journal*, 3 May 1952). The condition is rare and, as the author points out, is completely omitted from most standard textbooks, but in my experience it is by no means such a rarity as this article portrays and most gynaecologists will probably meet with one or two cases each year, the great majority resulting from malignant disease. Not all will be in agreement with Dr. Strasheim's views on the management of small fibroids at or about the climacteric. He writes: 'One must once again stress the extreme danger of leaving a myomatous uterus at or about the climacteric'; and again: 'Admittedly small, symptomless fibroids can be left alone, but then only if continued and periodical examinations can be carried out'. It seems to me these two statements are in conflict as 'the extreme danger' we are considering is sarcomatous change. Continued and periodic examinations can be of little help as it has been shown that rapid enlargement of a fibroid is only a rare sign of sarcomatous change.¹ Also, once malignant change has taken place treatment is virtually too late for the prognosis of even the smallest growths completely removed and irradiated, is fraught with disappointment.

The crux of the problem is whether the risk of sarcomatous change in fibroids at or about the climacteric is a greater threat to the patient's life than routine hysterectomy for all fibroids diagnosed at that time. Now the incidence of sarcomatous change in myomas has been estimated by Emil Novak as 0.56% in 6,981 cases examined histologically.² One must therefore assume that the incidence for malignant change in all myomas, many of which are undiagnosed, is much lower than Novak's figure, possibly in the region of 0.2%.

On the other hand the risk of either total or subtotal hysterectomy is considerable, chiefly because the incidence of fatal pulmonary embolism has not markedly decreased in the last decade. A round figure of 0.5% is probably a conservative estimate of the present-day risk in the best Clinics.

The following mortality rates are of interest:
Samaritan Hospital, London: Total, 0.4%; Subtotal, 1.3%.
Mayo Clinic: Total, 0.6%; Subtotal, 0.7%.

Chelsea Hospital, London: Total, 1.5%; Subtotal, 1.4%.³
It would seem, therefore, that routine hysterectomy for fibroids at or about the menopause is not justified.

Dr. Strasheim recommends hysterectomy if the uterus is larger than an 8-weeks' pregnancy at menopausal age. With this I agree but not because of the danger of sarcomatous change, which is no greater than with smaller fibroids.

A uterus enlarged to this extent, if not causing symptoms from its size at the time (backache, bearing-down pain, urinary troubles, etc.) will be very likely to do so as the menopausal relaxation of the pelvic ligaments progresses and there is some justification for its removal.

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Bryan Murless, F.R.C.S., M.R.C.O.G.

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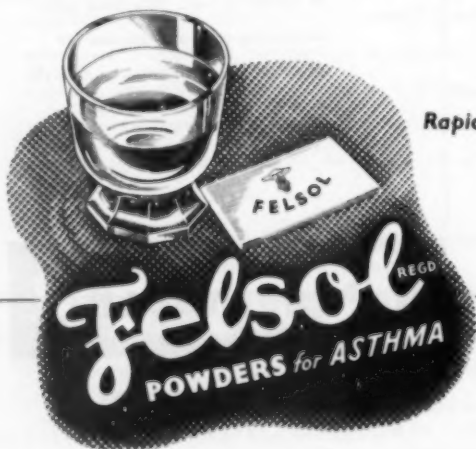
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In a case of this kind — in fact, whenever a patient manifests blood impoverishment and debility — there is need for the valuable tonic ingredients contained in Waterbury's Compound. Waterbury's Compound contains products obtained by the enzymatic action of pancreatic ferments on cod liver oil, livers and spleens, malt extracts and hypophosphites. It is produced in a palatable form and can be administered with every confidence by the practitioner.

WILLIAM R. WARNER & CO. (PTY) LTD.,
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COMPOUND**

66 E.

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(TRADE-MARK REGISTERED U.K., U.S. PATENT OFFICE)

DIAPHRAGMATIC MUSCLE EXTRACT
CLINICALLY PROVEN

- ANGINA PECTORIS
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- DISORDERS MARKED BY
IMPAIRED CIRCULATION
- PERIPHERAL VASCULAR DISEASE

etc., etc.

SUPPLIED IN BOXES OF 1 c.c. AND 2 c.c. AMPOULES FOR
PARENTERAL ADMINISTRATION

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Travel is a Wonderland.

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... that the average main line passenger train is made up of 15 vehicles with a gross weight of 600 tons.



... that you can send 60 lb. of luggage free by rail when you fly on the internal services of South African Airways. This is in addition to the 40 lb. you take with you in the aircraft.



... that the distance covered by the motor coach service between Cape Town and Durban is no less than 1,152 miles — about the same distance as from London to Warsaw!

SOUTH AFRICAN RAILWAYS SOUTH AFRICAN AIRWAYS ROAD MOTOR SERVICES

INK 6

The Medical Association of South Africa Die Mediese Vereniging van Suid-Afrika

AGENCY DEPARTMENT : AGENTSAP-AFDELING

JOHANNESBURG

Medical House, 5 Esselen Street. Telephones 44-9134-5, 44-0817
Mediese Huis, Esselenstraat 5. Telefoon 44-9134-5, 44-0817

MEDICAL EQUIPMENT

- (1/04) MacPhail-Strauss Electro Convulsant Unit. £90.
(1/026) B.G.E. 'Hanovia' Ultraviolet lamp. Good condition. £25.
(1/029) Examination Couch. £11.
(1/030) Cooke, Troughton & Simms Microscope in excellent condition. £40.
(1/031) Siebert Microscope, mechanical stage, 3 eye-pieces, oil immersion lens. £50.
(1/032) Spare oil immersion lens. £7 10s.
(1/033) Zeiss Microscope, 3 eye-pieces. Condition as new. £55.

LOCUM POSTS AND ASSISTANTSHIPS AVAILABLE PLAASVERVANGER- EN ASSISTENTSKAPPE BESKIKBAAR

- (L/V212) Eastern Transvaal. Locum required for July. Easily run dispensing practice, very little night work. Terms: £2 2s. p.d. all found, plus car allowance to be arranged.
(L/V231) O.F.S. For the month of July. Locum required for private practice with D.S. appointment. Terms: £2 2s. per day, free board and lodging and car allowance.
(L/V233) S.W.A. Locum required from 1 June till end January 1953. Subject to two months' notice either side. Salary £75 p.m., plus all found. Bilingual, single man preferred.
(L/V237) O.F.S. Locum required for month of July. Must have own car. Terms: £2 12s. 6d. per day, plus board and locomotion allowance.
(L/V236) Transvaal town, near Johannesburg. Locum required for 3 weeks, starting 1 July. Salary and allowances to be arranged.

KAAPSTAD : CAPE TOWN

Posbus 643, Telephone 2-6177 : P.O. Box 643, Telephone 2-6177

PRAKTYKE TE KOOP : PRACTICES FOR SALE

- (746) Large dispensing practice, mainly non-European. Average annual cash receipts approx. £5,200. £5,500 required for premium, drugs and surgery furniture. Details on application.
(1022) Cape Town Suburb. Old-established practice. Premium required £1,750. Terms available. Details on application.

NURSING HOME FOR SALE

- (1020) As going concern in large centre. Details on application.

ASSISTENTE/PLAASVERVANGERS VERLANG ASSISTANTS/LOCUMS REQUIRED

- (960) Eastern Province hospital town. As soon as possible, an assistant with view to partnership. Car essential but would not normally be required for practice. Single man preferred but not essential. Remuneration to be arranged.
(809) Gentile assistant for Transkei general practice with D.S. appointment. Single man preferred. Excellent opportunity to gain sound experience. Salary to be arranged.
(1057) Cape Town Suburbs from mid-July for 14 days. Industrial practice.
(1036) Northern Cape. From approx. 1 July for 3-4 weeks. Terms £2 2s. per day, plus all found. Car with driver provided.
(1040) Cape Town Suburb. From 2 July for 3 weeks. £2 10s. p.d. plus all found. Car provided.
(1041) East Griqualand. Month of July. Salary £80, plus board and lodging and rail fare or equivalent in cash. Own car preferable but not essential.
(1030) Western Province hospital town. From approximately 25 June for 6 weeks. Partnership practice. £2 12s. 6d. p.d. plus car allowance and board and lodging.
(1043) Kaapstad-Noordelike Voorsteed. Vanaf ongeveer 18 Junie tot en met 14 Julie. £2 2s. p.d. plus losies. Indien nodig word kar voorsien, andersins kartoele. Indien nodig word kar voorsien, andersins kartoele.
(1054) Westelike Provinsie vir maand vanaf 27 Junie.
(1055) Westelike Provinsie. Vanaf 23 Junie vir 1 week.

DURBAN

112 Medical Centre, Field Street. Telephone 24049

PRACTICES FOR SALE : PRAKTYKE TE KOOP

(PD6) Radiological practice, established 1923, in large coast city. Equipped for diagnosis, superficial and deep X-ray therapy and also superficial radium therapy. Extensive ground-floor rooms to be taken over on long lease. Premium required £6,750 cash, or terms arranged under suitable guarantees. For immediate sale.

(PD7) Solus prescribing practice on Natal South Coast. Scope for Native practice which at present is discouraged. Hospital facilities available at Port Shepstone Hospital, approximately 10 miles from consulting rooms. Premium required £2,500 which includes instruments, drugs, and furniture. Cash is preferred, but terms could be discussed. It is preferred not to sell this practice before the end of June 1952, but introduction could commence without delay and principal will allow half the net income. No appointments held. House is for sale at £4,500, partly furnished, but is not part of the practice.

(PD8) Natal South Coast practice. Would suit retired doctor. European population approximately 100. 31 miles from Bizana, 22 miles from Margate. Premium required £400, includes a good stock of drugs, dressings, instruments and surgery furniture. House for sale £1,800, including stand of $\frac{1}{2}$ morgen. For immediate sale.

(PD9) In large coastal City. Specialist in Physical Medicine wishes to dispose of private practice immediately. Centrally situated Rooms, full equipment and staff including Physiotherapists to be transferred.

(PD10) General Practice Natal Inland City. European and non-European patients. Scope for midwifery and surgery. Premium required £1,250, cash preferred but terms will be considered. For immediate sale.

LOCUM REQUIRED

For month of July. General Country Practice in Zululand £3 3s. per day plus £5 car allowance. Locum must possess his car. Afrikaans essential.

Mines Benefit Society

VACANCY FOR MEDICAL OFFICER FOR THE VENTERSPOST AREA

Applications are invited for the appointment as medical officer to the Society in the Venterspost/Libanon area. The salary to be paid is on the scale £1,000 x 50—£1,250 per annum; the starting notch will depend on the successful applicant's experience and qualifications. A travelling allowance will be paid at the rate of £30 per annum during such time as the medical officer is on duty and travelling in the area.

In addition to the remuneration already mentioned the incumbent will be entitled to receive one half of the fee of ninepence a member a month paid by the Rand Mutual Assurance Company for attendance in cases of mine accident. The number of members in the area in respect of which this fee is payable is at present 1,285.

The successful applicant will be required:—

- To attend members and their dependants resident on the mine properties and in the vicinity, affording to them in case of need such medical and surgical service as are ordinarily rendered by a general practitioner.
- To provide and maintain at his own cost the transport necessary for the performance of his duties.
- To commence duties on 1 August 1952.
- To become a member of the Mines Benefit Society Staff Fund.

The successful applicant will not be permitted to indulge in private practice.

Note: The services to be given include attendance, when sought, at confinements of members' wives. For such services a fee not exceeding five guineas may be charged by the medical officer.

Applicants should state in writing, to reach the undersigned not later than 21 June 1952:—

- Age;
- marital state;
- qualifications;
- experience, with special reference to experience in surgery;
- whether bilingual.

P.O. Box 8603
Johannesburg

O. Knox
Acting General Secretary

South African Coal, Oil and Gas Corporation Limited (S A S O L)

VACANCY: PART-TIME MEDICAL OFFICER

Applications are invited from medical practitioners for the post of part-time medical officer at Sasolburg (near Coalbrook, O.F.S.). The duties are mainly the medical and surgical care of Native employees. Duties will commence as soon as possible and further details may be obtained on request.

Applications stating age, qualifications, experience, and marital state should reach the Secretary, Sasol, Private Bag 14, Johannesburg, not later than 27 June 1952.

Suid-Afrikaanse Steenkool-, Olie- en Gaskorporasie Beperk (S A S O L)

VAKATURE: DEELTYDSE MEDIESE PRAKTIJSYN

Aansoeke word ingewag van mediese praktisyne om die pos van deeltydse mediese beampte. Die pligte behels hoofsaaklik mediese en heelkundige dienste aan natuurlewerknemers van Sasol op Sasolburg, naby Coalbrook, O.V.S. Dienste moet so spoedig moontlik aanvaar word. Nadere besonderhede is verkrygbaar op versoek.

Aansoeke met vermelding van ouderdom, kwalifikasies, ondervinding en huwelikstaat moet die Sekretaris, Sasol, Privaatsak 14, Johannesburg, nie later as 27 Junie 1952 bereik nie.

City of Durban

VACANCY FOR PART-TIME CLINICAL MEDICAL OFFICER (FEMALE)

GREY STREET NATIVE WOMEN'S HOSTEL (MUNICIPAL NATIVE ADMINISTRATION DEPARTMENT)

Applications are invited from registered female medical practitioners for the abovementioned part-time appointment in the Municipal Native Administration Department.

The duties appertaining to the position involve attendance at the Municipal Native Women's Hostel, Grey Street, for the purpose of conducting a general clinic for the residents of the Hostel. Clinic sessions will be held once weekly between the hours of 7 and 9 p.m. on a day to suit the convenience of the successful applicant.

The remuneration will be at the rate of £2 2s. per session. Termination of appointment will be subject to three calendar months' notice on either side.

Applications stating age, marital state, qualifications and experience should reach the Acting Manager, Municipal Native Administration Department, 132 Ordnance Road, Durban, not later than 12 noon on Wednesday, 2 July 1952.

Personal canvassing for appointment is prohibited and proof thereof will disqualify a candidate—*vide* Council's Standing Order No. 1.

John McIntyre
Town Clerk

Town Clerk's Office
Durban
24 May 1952

Required

Assistant wanted for Cape Town practice, part-time or full-time. State age, experience and salary required and whether car available. Write 'A.M.B.', P.O. Box 643, Cape Town.

Wanted

Post wanted as assistant or locum in Cape Town area. Write 'A. L. S.', P.O. Box 643, Cape Town.

South African Railways & Harbours Sick Fund

APPOINTMENT OF RAILWAY MEDICAL OFFICER : KOSTER

Applications are invited from registered medical practitioners for the position of Railway Medical Officer, Koster, and for section of railway line Magaliesburg (exclusive) to Mazista (exclusive), at a salary of £248 per annum, plus the fees and allowances prescribed by the Regulations of the Sick Fund, and with the right of private practice.

The salary will be subject to adjustment in accordance with the census of members to be taken on 1 April of each year.

The appointment will be made in terms of the Regulations of the Fund, and will be subject to termination on 4 months' notice being given by either side.

The successful applicant will be required to reside at Koster, to take up the appointment on a date to be arranged, and to carry out his duties in accordance with the Regulations of the Fund.

Applications should reach the District Secretary, Western Transvaal District Sick Fund Board, Room 342, Third Floor, New Station Buildings, Johannesburg, not later than 5 July 1952, and should state:—

1. Full name.
2. Qualifications (when and where obtained).
3. Experience (when and where obtained).
4. Date of birth.
5. Country of birth.
6. Whether single or married.
7. Whether fully bilingual.
8. Whether South African citizen.
9. What Government appointment, if any, is held.

Canvassing by or on behalf of any applicant is liable to disqualify such applicant.

Any further particulars may be obtained from the District Secretary at the above address, on application.

Johannesburg
14 June 1952

P. J. Klem
General Secretary

Public Service Commission

VACANCIES IN THE PUBLIC SERVICE

1. The attention of medical practitioners, registered with the South African Medical and Dental Council, is drawn to an advertisement appearing in the *Government and Provincial Gazettes* of this week, inviting applications for the undermentioned posts.

Post	Department	Salary Scale
Medical Inspector of Schools	Transvaal Provincial Administration	£950 x 50—1,300
District Surgeon Grade III	Health (Louis Trichardt)	£900 x 50—1,150

2. In addition to salary a cost-of-living allowance at the rate of £320 per annum (married) and £100 per annum (single) is payable at present.

3. It is emphasized that full and detailed particulars of qualifications and previous experience must be furnished, but original certificates and testimonials should not be submitted. Application forms (Z.83 and P.S.C. 8 (a)) are obtainable from the Secretary, Public Service Commission, Pretoria, to whom filled-in forms must be addressed.

4. The closing date for the receipt of applications is 28 June 1952. 35606

Provincial Administration of the Cape of Good Hope

HOSPITALS DEPARTMENT

HOSPITAL BOARD SERVICE: VACANCIES

1. Applications are invited for the following vacant posts in the Hospital Board Service:—

Institution	Post	Salary scale	Closing date	Applications must be addressed to:
Frere Hospital, East London	Medical Practitioner, Grade A (Casualty Officer)	£500-600-660-720 p.a.	23.6.52	The Medical Superintendent, Frere Hospital, East London.
Victoria Hospital, Lovedale	Medical Practitioner, Grade A	£500-600-660-720 p.a.	30.6.52	The Medical Superintendent, Victoria Hospital, Lovedale.
Frere Hospital, East London	Junior Resident Medical Officer	£240 p.a. plus board and quarters (£72 p.a.) and laundering (£6 p.a.)	30.6.52	The Medical Superintendent, Frere Hospital, East London.
Grey Hospital, King William's Town	Junior Resident Medical Officer	ditto	30.6.52	The Medical Superintendent, Grey Hospital, King William's Town.

2. The conditions of service are prescribed in terms of the Hospital Board Service Ordinance No. 19 of 1941, and the regulations framed thereunder.

3. In addition to the scale of salary indicated a cost-of-living allowance at rates prescribed from time to time by the Administrator is payable to whole-time officials and employees.

4. The successful candidates, if not already in the Hospital Board Service, will be required to submit satisfactory birth and health certificates.

5. Application must be made on the prescribed form (Staff 23), which is obtainable from the Director of Hospital Services (P.O. Box 2060), Provincial Building, Wale Street, Cape Town, or from the Branch Representatives of the Hospitals Department at Cape Town (P.O. Box 1487), Port Elizabeth (P.O. Box 80), East London (P.O. Box 13), Kimberley (P.O. Box 618) and Umtata (P.O. Box 202), or from the Medical Superintendent of any Provincial Hospital or Secretary of any School Board in the Cape Province.

6. Candidates must state the earliest date on which they can assume duty. Y267586

Johannesburg Municipal Employees' Sick Benefit Society

Applications are invited for the post of part-time Dental Surgeon. Applicants must be registered dentists, bilingual and must have suitable premises to cater for approximately 2,800 members and their dependants.

The salary offered is £175 per month.

Further details can be obtained from the undersigned.

P. J. Uys
Secretary

401/422 P.F.A.C. Buildings
15 de Villiers Street
P.O. Box 2626
Johannesburg

Provinsiale Administrasie van die Kaap die Goeie Hoop

HOSPITAALDEPARTEMENT

HOSPITAALRAADSDIENS: VAKATURES

1. Aansoeke word ingewag om die volgende vakante poste in die Hospitaalraadsdiens:—

Inrigting	Pos	Salarieskaal	Sluitingsdatum	Aansoeke moet gerig word aan:
Frere-hospitaal, Oos-Londen	Geneesheer, Graad A (Ongevalle Beampte)	£500-600-660-720 p.j.	23.6.52	Die Mediese Superintendent, Frere-hospitaal, Oos-Londen.
Victoria-hospitaal, Lovedale	Geneesheer, Graad A	£500-600-660-720 p.j.	30.6.52	Die Mediese Superintendent, Victoria-hospitaal, Lovedale.
Frere-hospitaal, Oos-Londen	Junior Inwonende Mediese Beampte	£240 p.j. plus kos en inwoning (£72 p.j.) en klerewas (£6 p.j.)	30.6.52	Die Mediese Superintendent, Frere-hospitaal, Oos-Londen.
Grey-hospitaal, King William's Town	Junior Inwonende Mediese Beampte	ditto	30.6.52	Die Mediese Superintendent, Grey-hospitaal, King William's Town.

2. Die diensvoorwaardes word voorgeskryf ingevolge die Ordonnansie op Hospitaalraadsdiens nr. 19 van 1941, en die regulasies wat daarkragens opgestel is.

3. Benewens die salarisskaal soos aangedui, is 'n lewenskoste-toelae betaalbaar aan voltydse beamptes en werknemers teen bedrae wat van tyd tot tyd deur die Administrateur vasgestel word.

4. Die geslaagde kandidaat indien nie reeds in die Hospitaalraadsdiens nie, moet bevredigende geboorte- en gesondheid-sertifikate indien.

5. Aansoek moet gedoen word op die voorgeskrewe vorm (Staf 23) wat verkrygbaar is by die Direkteur van Hospitaaldienste, Posbus 2060, Provinsiale Gebou, Waalstraat, Kaapstad, of by die Takvertegenwoordigers van die Hospitaaldepartement te Kaapstad (Posbus 1487), Port Elizabeth (Posbus 80), Oos-Londen (Posbus 13), Kimberley (Posbus 618) en Umtata (Posbus 202) of by die Mediese Superintendent van enige provinsiale hospitaal of by die Sekretaris van enige Skoolraad in die Kaap-provinsie.

6. Kandidate moet die vroegste datum meld waarop hulle diens kan aanvaar. Y267586

Interns Required

Rural mission hospital in Transkei, modern, well equipped, handling medical, surgical and obstetrical cases, requires one senior intern with some surgical experience and one junior intern. To commence duties on or about 1 July 1952. Apply: Medical Superintendent, Nessim Knight Hospital, Sulekama, Qumbu, C.P.

BRASS PLATES

TO MEDICAL COUNCIL SPECIFICATION

VICTOR C. GLAYSHER

165 BREE STREET
CAPETOWN

PHONE
2-5111

Provincial Administration of the Cape of Good Hope: University of Cape Town

JOINT MEDICAL STAFF FOR GROOTE SCHUUR AND OTHER TEACHING HOSPITALS: VACANCIES

1. Applications are invited from registered medical practitioners (registered specialists) for appointment to the following posts:—

Department of Obstetrics and Gynaecology—1 post of Medical Practitioner, Grade G—salary £182 per annum per session (5 sessions).

Department of Ear, Nose and Throat—1 post of Medical Practitioner, Grade G—salary £182 per annum per session (2 sessions).

2. The conditions of service are prescribed in terms of the Hospital Board Service Ordinance No. 19 of 1941, as amended, and the regulations framed thereunder.

3. The Joint Medical Staff will be required to serve jointly the Provincial Administration of the Cape of Good Hope and the University of Cape Town.

4. Candidates are required to have not less than three years' experience after registration as a specialist in the speciality in which the vacancy exists.

5. (a) A session shall be 4 hours per week not necessarily continuous of clinical and/or teaching work.

(b) Candidates must state the maximum number of sessions which they would on appointment, be prepared to undertake.

6. The successful candidates will be required to submit satisfactory birth and health certificates.

7. Applications must be made on the prescribed form Staff 23 which is obtainable from the Director of Hospital Services, P.O. Box 2060, Provincial Building, Wale Street, Cape Town, or from the Branch Representatives of the Hospitals Department at Cape Town (P.O. Box 1487), Port Elizabeth (P.O. Box 80), East London (P.O. Box 13), Kimberley (P.O. Box 618) and Umtata (P.O. Box 202), or from the Medical Superintendent of any Provincial Hospital or Secretary of any School Board in the Cape Province.

8. The completed application forms must be addressed to the Director of Hospital Services, P.O. Box 2060, Cape Town, and must reach him not later than 30 June 1952. Candidates must state the earliest date on which they can assume duty.

Y 267594

City of Johannesburg

VACANCY

Applications are invited for the following vacant position in the City Health Department:

Medical Officer, Waterval Hospital: Grade 10 (£996—12—£1,020 per annum), plus free quarters and laundry.

In addition to the basic salary a cost-of-living allowance is paid in accordance with the Council's resolution of 25 August 1942, as amended, at present £25 12s. 2d. per month.

Applicants must be medical practitioners registered to practise in South Africa.

Details of duties and conditions of service will be supplied on application to the Medical Officer of Health, P.O. Box 1477, Johannesburg.

The successful applicant will be required to undergo a medical examination and become a member of the Council's Pension Fund.

Personal canvassing for appointment in the gift of the Council is strictly prohibited. Proof thereof will disqualify the candidate for appointment.

Applications in the candidate's own handwriting on special forms obtainable from the Central Staff Office, Room 223, Municipal Offices, must be placed in the box in Room 223, Municipal Offices, or posted so as to reach the undersigned not later than 4 p.m. on 23 June 1952.

Brian Porter
Town Clerk
662/1176

Adv. 719

Provinsiale Administrasie van die Kaap die Goeie Hoop: Universiteit van Kaapstad

GESAMENTLIKE MEDIESE PERSONEEL VIR GROOTE SCHUUR EN ANDER OPLEIDINGSHOSPITALE: VAKATURES

1. Aansoeke word ingewag van geregistreerde geneesher (geregistreerde spesialiste) vir aanstelling tot die volgende poste:—

Departement van Vrouesiektes en Verloskunde—1 pos van Geneesheer, Graad G—salaris £182 per jaar per sessie (5 sessies).

Departement van Oor, Neus en Keel—1 pos van Geneesheer, Graad G—salaris £182 per jaar per sessie (2 sessies).

2. Die diensvoorwaardes word voorgeskryf ingevolge die Ordonnansie op Hospitaalraadsdiens nr. 19 van 1941, soos gewysig, en die regulasies wat daarkragens opgestel is.

3. Van die Gesamentlike Mediese Personeel sal vereis word om die Provinsiale Administrasie van die Kaap die Goeie Hoop en die Universiteit van Kaapstad gesamentlik te dien.

4. Kandidate moet minstens drie jaar ondervinding na registrasie as 'n Spesialis in die spesialiteit waarin die vakature bestaan, opgedoen het.

5. (a) 'n Sessie is 4 uur per week in verband met kliniese en/of opleidingswerk maar is nie noodwendig onafgebroke nie.

(b) Kandidate moet die maksimum getal sessies wat hulle by aanstelling gewillig sal wees om by te woon, meld.

6. Die geslaagde kandidate indien nie reeds in die Hospitaalraadsdiens nie, moet bevredigende geboorte- en gesondheidsertifikaat indien.

7. Aansoeke moet gedoen word op die voorgeskrewe vorm (Staf 23) wat verkrygbaar is by die Direkteur van Hospitaaldienste, Posbus 2060, Provinsiale Gebou, Waalstraat, Kaapstad, of by die Takvertegenwoordigers van die Hospitaaldepartement te Kaapstad (Posbus 1487), Port Elizabeth (Posbus 80), Oos-Londen (Posbus 13), Kimberley (Posbus 618) en Umtata (Posbus 202) of by die Mediese Superintendent van enige provinsiale hospitaal of by die Sekretaris van enige Skoolraad in die Kaapprovinsie.

8. Die ingevulde aansoekvorms moet aan die Direkteur van Hospitaaldienste, Posbus 2060, Kaapstad, gerig word en moet hom uiters op 30 Junie 1952 bereik. Kandidate moet die vroegste datum meld waarop hulle diens kan aanvaar.

Y 267594

Cape Provincial Administration

HOSPITALS DEPARTMENT

VACANCY: HONORARY MEDICAL STAFF

Applications are invited from registered medical practitioners under the age of 60 years for appointment to the under-mentioned post on the honorary staff of the Provincial Hospital, Port Elizabeth:

Clinical Assistant to the Department of Obstetrics and Gynaecology.

The appointment is subject to the Hospitals Ordinance No. 18 of 1946 (Cape), as amended, and to the rules and regulations of the Department.

Applications, containing full particulars of qualifications, etc., must be addressed to the Medical Superintendent of the Provincial Hospital, Port Elizabeth, to reach his office not later than 25 June 1952.

C. G. Keyter
Branch Representative
3413

Cuthbert's Building
P.O. Box 80
Port Elizabeth
27 May 1952



In this room of the Sterile Area at our Speke premises operators are filling penicillin into vials under the most rigorous aseptic conditions.

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SPEKE

ENGLAND

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